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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

WILLIAM C. STADIE

VINCENT P. DOLE

HUGH J. JEWETT

THYROID DISEASES IN CHILDREN AND ADULTS

Transcription of a Panel Meeting

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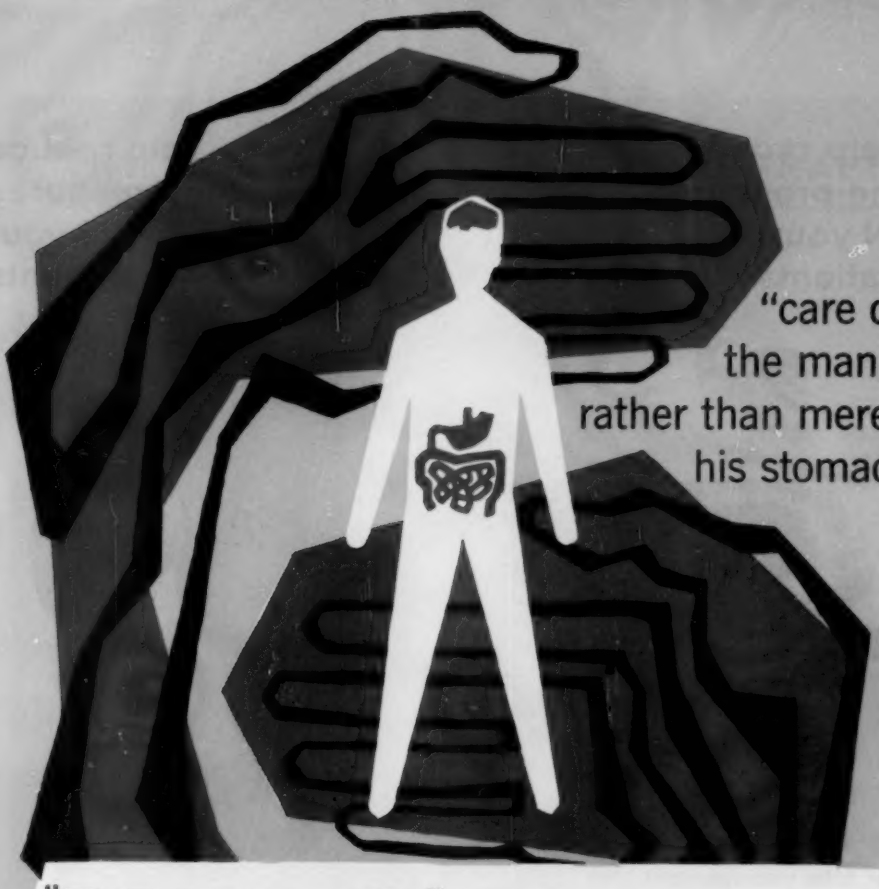

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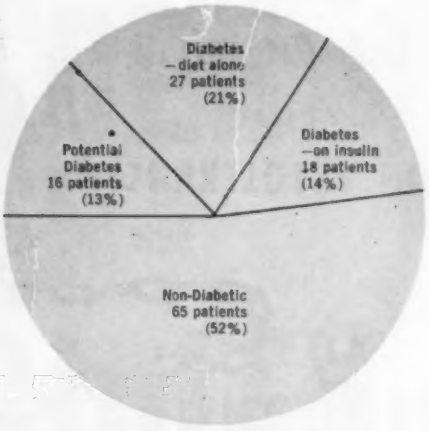

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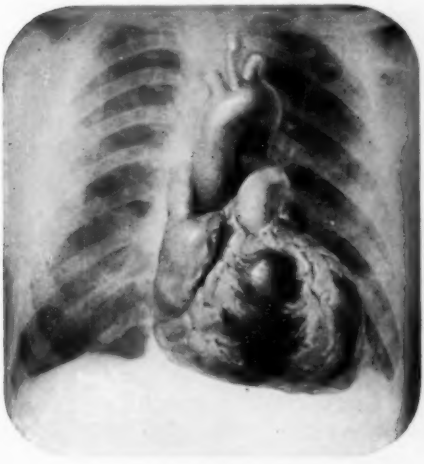

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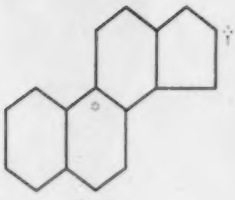

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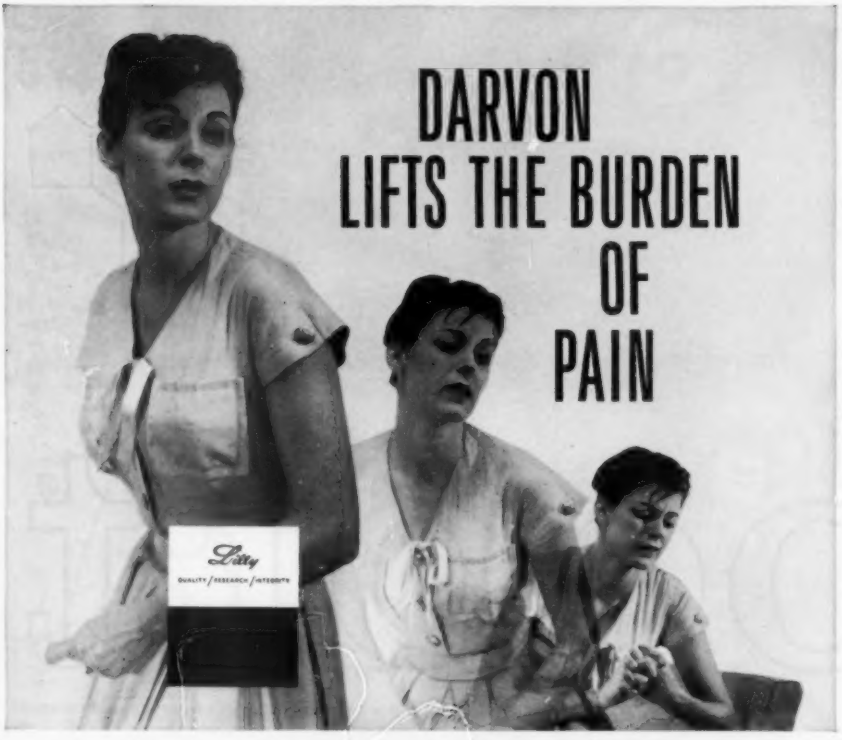

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 34, NO. 1 JANUARY 1958

INTRODUCTORY REMARKS*

First Annual Postgraduate Week

ROBERT L. LEVY

President, The New York Academy of Medicine

THERE is at present under way a survey of the entire organization of The New York Academy of Medicine. A statement outlining its purposes and scope appeared in the October issue of the Bulletin, published last week. The ultimate aim of this thorough self-examination is to make more effective, in terms of current thinking, the various services rendered. It is logical to assume that the Academy should find its field of greatest usefulness, to the medical profession and to the community, in filling needs which cannot be fully met by other agencies.

One of the important functions of the Academy lies in the domain of graduate study. The Committee on Medical Education, under the chairmanship of Dr. Louis J. Soffer, has been keenly aware of the many excellent courses and exercises offered by the medical schools and hospitals of New York. It appeared likely, therefore, that a relatively short program, embracing diverse topics, and including both basic and

* Made at the first lecture session of the Postgraduate Week, replacing the *Graduate Fortnight* of former years, of The New York Academy of Medicine, October 7, 1957.

clinical aspects of disease, might be met with greater enthusiasm than a longer session covering a more limited area. This formula for the first Postgraduate Week, which replaces the former Graduate Fortnight, is frankly an experiment and is designed to appeal not only to mature practitioners but also to the younger groups working in hospitals and research laboratories. The Academy wants particularly to enlist the interest, in all of its affairs, of physicians still in training, for they are the potential leaders of the future.

On a previous occasion it was suggested that, to attract an eager audience, "there must be fostered an atmosphere of genuine intellectual interest spiced with a practical flavor". Surely the title "Research Contributions to Clinical Practice" promises to meet these specifications. On behalf of the Academy, I bid you welcome, with the hope that you will enjoy this week and will feel that the time has been spent profitably. Comments, in writing, favorable or otherwise, will be received gratefully and may be sent to the Director, Dr. Howard Reid Craig, at this address.

Fully responsible for the high quality of this year's Postgraduate Week are the members of the Program Committee, chaired by Dr. Isidore Snapper. They have given much time and thought to planning, and have assembled a galaxy of star performers. It now gives me pleasure to present Dr. Snapper and to turn the meeting over to his wise guidance.

ASPECTS OF CARBOHYDRATE AND PHOSPHATE METABOLISM IN DIABETES*

The Wesley M. Carpenter Lecture

WILLIAM C. STADIE

Emeritus Professor of Research Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

I SHALL discuss three subjects in the field of diabetes:

1. The chemical structure of insulin;
2. The defect in carbohydrate metabolism in the diabetic animal;
3. Some recent work on phosphate metabolism in the diabetic cat.

1. THE STRUCTURE OF INSULIN

There are a group of hormones which are proteins of large molecular weight: for example, growth hormone, ACTH, and insulin. In the case of insulin, the molecular weight has a minimum value of about 6000 and the determination of the order in which the constituent amino acids are joined together in peptide linkage presents a difficult problem. Insulin is the only protein hormone whose structure is completely known. Most of the work in this field has been done by Sanger in England.

The general method of study is simple in principle but arduous in practice. Initial studies on insulin showed that it was composed of two large polypeptide chains named A and B respectively. The A chain had glycine as a terminal amino acid; the terminal amino acid of the B chain is phenyl alanine. The detailed structure of these chains is obtained by the following general method: By choice of the investigator, the chain is hydrolyzed to a varying extent by a variety of methods; for example, acid hydrolysis for different lengths of time; or by specific proteolytic enzymes such as pepsin, trypsin, chymotrypsin, or proteinases from bacteria or other sources. The resulting mixture may be composed of single amino acids, or dipeptides, tripept-

* Presented at The New York Academy of Medicine, October 8, 1957, at its Postgraduate Week, replacing the *Graduate Fortnight* of former years.

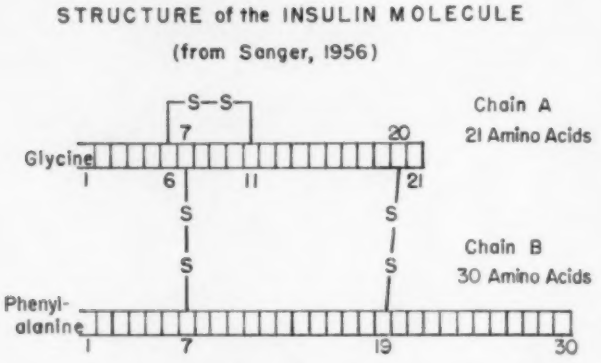

Fig. 1—Structure of the insulin molecule. (Data from Sanger, F. The structure of insulin, in *Currents in biochemical research, 1956.)*

ides, or longer polypeptides. This mixture is treated with fluorodinitrobenzene which combines with all terminal free amino groups including, of course, the newly formed ones. In this way strongly colored dinitrophenyl derivatives are formed which, after extraction with suitable solvents, may now be isolated in a pure state by appropriate methods of separation such as column or paper chromatography. Analytical methods are then used to identify the amino acids in the various fractions isolated. The terminal amino acid in each instance is easily recognized on account of the color of the dinitrophenyl derivative and, of course, indicates the site of cleavage by hydrolysis from the carboxyl group of the adjacent amino acid with which it was combined in peptide linkage. The various fractions are then split by further hydrolysis and again treated with dinitrofluorobenzene to form new dinitrophenyl derivatives. Separation of the new peptides is again done and the process of analysis repeated. A new set of peptide linkages is thus revealed. These manipulations are repeated over and over again until the knowledge obtained is sufficient to piece together the total structure of the protein. The method is prolonged and tedious requiring the isolation and analysis of hundreds of different peptides obtained by various methods of proteolysis.

The structure of insulin according to Sanger is shown in Figure 1. Each block represents one amino acid. There are 16 different amino

acids in the molecule of insulin, but the total number of residues is 51. The minimum molecular weight is about 6000. The A chain contains 21 amino acids, glycine being the terminal acid; the B chain contains 30 amino acid residues, the terminal acid being phenyl alanine. These chains are linked together by two disulfide bridges derived from the amino acid cysteine occupying positions 7 and 20 on the A chain and 7 and 19 on the B chain respectively. In addition, there is an intrachain disulfide bridge indicated as shown between the 6th and 11th amino acid on the A chain.

Practically nothing is known about the relation of the structure to the metabolic activity of insulin. Minor variations in the make up of the two chains have been observed in insulins obtained from different species with no apparent variation in the physiological activity of the hormone. The A and B chains alone have no metabolic action. Apparently the disulfide bonds are of great significance because if they are oxidized the insulin loses its biological activity. Indeed, the relation of the structure of a protein hormone to its biological action is a fascinating field for future research.

Isotopic Insulin: A short discussion of isotopic insulin is in order here. There are a considerable number of problems in which the availability for experimental purposes of isotopic insulin would be of great advantage. For example: 1) The locus of insulin following equilibration of tissues *in vitro* or after intravenous injection in the intact animal, could easily be determined. 2) Isotopic insulin preparations are available with such high radioactivities that 10^{-11} gm. or about a millionth of a unit can easily be determined. Experiments relating metabolic activity to minute amounts of insulin in tissue are thus possible. 3) Experiments designed to illume the field of the metabolism of insulin itself can be done by following concentrations in tissues and urine after injection into animals under different experimental conditions.

There are three ways in which insulin can be converted into radioactive forms: 1) By iodination with I^{131}. This is easily accomplished by incubating the insulin solution under suitable conditions with I^{131} followed by dialysis to remove excess free iodine. The iodine combines with the carbon atoms of the benzene ring of tyrosine. In practice only about one out of a thousand of the tyrosine residues in the insulin molecule are iodinated. The metabolic activity of the iodinated insulin is unchanged. However, following injection into the intact animal, the

iodine may be rapidly separated from the insulin. Presumably this separation occurs in the kidney, the iodine being rapidly excreted as iodide ion or contained in small peptides which, unlike insulin, are dialyzable. 2) By the formation of sulfate ester using $H_2S^{35}O_4$ with the alcoholic group of threonine. This preparation is somewhat more difficult than iodination. But the preparation has a half life of about 80 days compared with 8 days in the case of I^{131}. Furthermore, availability of two different radioactive isotopic insulins makes it possible to check observed phenomena in two ways. As in the case of I^{131} insulin, S^{35} insulin appears not to have lost any of its metabolic activity. 3) The third method of preparing radioactive insulin is to incorporate C^{14} into the insulin molecule. This is accomplished by preparing cultures of pancreatic tissue in a medium containing some amino acid containing C^{14}, e.g., C^{14} alanine or glycine. The tissues are then worked up for the isolation of the newly formed insulin containing the isotopic amino acid. Small amounts of insulin containing relatively low amounts of radioactivity have been prepared by this method but the usefulness of the method is limited to a study of the structural characteristics of insulin.

2. Carbohydrate Metabolism in the Diabetic Animal

The understanding of the symptoms of a metabolic disease such as diabetes is dependent upon a knowledge of the chemical reactions which underlie biological activity. A requisite for this understanding is a knowledge of the functions of the enzymes and co-enzymes which bring about a series of orderly molecular changes in the available foodstuffs within the cell. Cellular homeostasis can then be discussed in terms of the complex reactions catalyzed by the cellular enzyme systems. When these finely integrated chemical reactions are disturbed, there is a departure from normal metabolic function; the abnormal condition which results is the disease. But enzymatic action is influenced by a great variety of endocrines arising, for example, from the alpha or beta cells of the islands, from the pituitary, adrenals, etc. In diabetes, these considerations generate two separate problems for investigation. The first is the problem of the metabolic defect, that is, the recognition of the nature of the disturbances of the complex interrelations of enzymes, co-enzymes, and hormones which occur in this disease. The second is the problem of the mode of action of insulin; that is, the description of the mechanisms by which insulin eliminates these metabolic defects.

Thirty-five years have elapsed since the discovery of insulin; nevertheless, these two problems are still obscure and continue to be fields for active experimentation and speculation. I propose to discuss in this paper some experiments designed to illuminate these two areas. A pattern begins to reveal itself and I shall undertake to describe this pattern as I see it.

One more remark of a general character needs to be made, I believe, before plunging into the discussion of details of metabolism in diabetes. Study of the diabetic defect and the mode of action of insulin can be approached in two ways. The first is to couch the discussion in terms of specific chemical reactions. For example, we may ask: Is the reaction:

$$\text{Glucose} + \text{phosphate} = \text{glucose-6-phosphate}$$

that is, the hexokinase reaction, impaired in the diabetic state? Or: Does insulin accelerate the reaction:

$$2 \text{ acetyl Co-A} = \text{butyryl Co-A}$$

a reaction necessary for the synthesis of higher fatty acids? Indeed, our knowledge of the metabolic aspects of diabetes is almost exclusively composed of the answers to innumerable questions of a similar character.

The second approach is to direct our speculations toward possible alterations of molecular configurations of tissue catalysts: For example, we may ask: Is insulin an integral part of an enzyme system so that the "fit" of some substrate is improved and catalysis is accelerated? Or: Does insulin become part of an electron chain so that an assumed impediment in electron flow is removed and therefore oxidation of some substrate is increased? This field of "molecular medicine" has scarcely been touched. Linus Pauling has made the initial explorations in his description of the molecular changes in hemoglobin occurring in sickle cell disease and other abnormal hemoglobin syndromes. Pauling[1] also speculated about the possible therapeutic elimination of the enzymatic defect which is at the basis of phenyl pyruvic oligophrenia. In diabetes, the only demonstration of what might be called a molecular phenomenon is the demonstration in our laboratory[2] that insulin is bound by tissues. In the rat diaphragm, the reaction is very rapid and the bound insulin exhibits all of its characteristic properties.

A short discussion of this phenomenon is appropriate here. The introduction of insulin labelled with radioactive iodine made it possible to measure with accuracy the minute amounts of insulin bound to

tissue. It was shown, for example, that the increased glycogen synthesis from glucose by the isolated rat diaphragm was proportional to the amount of insulin bound to the tissue. Thus, for the first time, the response of a tissue to a known amount of hormone in accelerating a specific chemical reaction was measured. Almost all the tissues of the body bind insulin but in different concentrations. The amount bound by muscle or liver tissues with high rates of metabolism, is high. The binding capacities of the structural elements of the liver, i.e., mitochondria, nuclear fraction, and microsomes, are different, indicating a specificity of the binding. The brain, which has never been shown to react to insulin, shows no bound insulin following intravenous injection of the hormone in the intact animal. This organ, then, appears to have a metabolism not requiring insulin.

In the case of the rat diaphragm studied *in vitro*, the behavior of the bound insulin is in complete accord with our knowledge of its action obtained in other ways. For example, the response to bound insulin is diminished in the alloxanized animal. It is also diminished by the injection of cortisone and growth hormone, which are known to be insulin antagonists. In the hypophysectomized rat, amounts of bound insulin which in the normal rat are without effect upon glucose uptake, have almost maximum effects. This is in accord with the well known insulin sensitivity of the hypophysectomized animal. Adipose tissue and lactating mammary gland also respond to bound insulin. The binding of insulin by tissues may have analogous implications to the binding of substrates by enzyme systems. For example, Stetten has attempted to calculate for insulin-tissue binding a constant similar to the Michaelis-Menten constant for enzyme-substrate binding. However, the full significance of the phenomenon remains to be worked out.

These concepts of the metabolic effects of insulin are necessarily complex but inevitably yield practical benefits. One recent practical benefit gained from the knowledge of the action of insulin accumulated during the past quarter century is the evaluation of the therapeutic usefulness of the hypoglycemic drugs recently introduced in the treatment of diabetes. The experimenter had available patterns of behavior of the metabolism of the mammalian organism in response to the administration of insulin. With this knowledge, similar experimental designs could be formulated for testing the action of the oral hypoglycemic drugs. Thus, within a relatively short space of time it was shown that

the responses of mammalian metabolism to the drugs were quite different from those of insulin. They were, therefore, not insulin substitutes but accessory agents which could be used with benefit in a limited number of cases.

Turning now to the discussion of metabolism in diabetes, there are two hypotheses which have been formulated to explain why the early steps in the metabolism of glucose are impaired in diabetes. The first metabolic reaction of glucose is a reaction with inorganic phosphate to form glucose-6-phosphate catalyzed by the enzyme hexokinase. This phosphorylation of glucose is a prerequisite for its further metabolism. Impairment of this reaction would necessarily bring to a halt all further metabolic reactions of the sugar. Experiments reporting inhibition of the hexokinase reaction in extracts of the muscles of diabetic animals have been reported, but these findings have not been confirmed. So far as muscle is concerned, it is now generally held that impairment of the hexokinase reaction does not play any role in the decreased ability of the muscle to metabolize glucose. However, this conclusion does not necessarily hold for the liver, and the possibility still remains that a defect of glucose metabolism in that organ might be due to deficient glucose-6-phosphate formation owing to an inhibition of hepatic hexokinase.

A second hypothesis concerning insulin action in muscle involves the role of the cell membrane in early glucose metabolism. This was first suggested by Hoeber[3] in 1927, who proposed a "membrane theory of diabetes". He said: "One thinks that an abnormal constitution of the cell membrane does not allow the simple sugars to reach their normal locus of breakdown. If one considers the above possibility we may substitute for the present theory of diabetes, which is based upon concepts of abnormal enzymatic activities, another theory, namely, the membrane theory of diabetes." Hoeber himself presented no experimental data to support this hypothesis and some 25 years passed before two investigators, Levine[4] of Chicago and Ross[5-7] of London, studied the possible role of permeability factors in diabetes, each approaching the subject from different points of view.

Levine's experimental design was simple in principle. First, he used the completely eviscerated dog. Second, he selected sugars, for example, galactose, which are not metabolized by these eviscerated animals. Using this experimental system, he calculated the volume of distribution of

sugars following intravenous injection from the constant levels of blood sugar established. He found, for example, in the case of galactose, that in the absence of injected insulin, the blood galactose levels established indicated a volume of distribution of 45 per cent of the body weight, approximately that of the extracellular space. In the same preparation, when insulin was simultaneously injected with the galactose, the volume of distribution was 70 per cent of the body weight, essentially that of body water. Levine concluded from these data that in the absence of insulin the galactose was practically excluded from the muscle cell. Following insulin injection the barrier which had excluded the sugar from the cell was eliminated; the galactose then distributed itself throughout the whole of body water. In similar experiments Levine studied other sugars and he divided them into two groups: 1) those which were nonresponsive to insulin, that is, the volume of distribution was unchanged by the injection of insulin; and 2) those sugars which were insulin responsive in that the volume of distribution was increased. In this latter group were placed d-galactose, l-arabinose and d-xylose. Levine called attention to the fact that the structures of these sugars with respect to carbons 1, 2, and 3, were similar and hence he concluded that the entrance of sugar into muscle "is governed by a transfer system which is specifically adapted with respect to chemical structure". Glucose itself cannot be used in Levine's eviscerated preparation because, unlike galactose, it is metabolized in the peripheral tissues. Therefore a constant blood level of glucose from which the volume of distribution can be calculated is not established. However, Levine included glucose in the insulin-responsive group because the structure of its first three carbon groups is similar to that of the sugars experimentally shown to be insulin responsive.

Ross at the London Ophthalmological Institute approached the subject in a different way. Initially he was interested in studying the rate of penetration of a variety of chemicals from the blood stream into the aqueous humor through the ciliary body. He calculated his results in terms of a "permeability constant" and he compared this constant with the relatively lipid solubility of the substance, that is, the ratio of its solubility in alcohol to its solubility in water. He found a striking correlation between these two variables. Those substances which had a high relative lipid solubility and therefore could be termed "lipophylic" had high permeability constants. Contrariwise, those that

TABLE I—TRANSFER OF GLUCOSE ACROSS BLOOD-AQUEOUS BARRIER IN RABBIT EYE
(Data from Ross, E. J., 1952)

	$1000\ k_{in}$
Normal	199 ± 36
Alloxanized (Blood glucose 400-500 mg %)	102 ± 10
Decrease	97 ± 38
	$t = 2.5$

had a relatively low lipid solubility and therefore might be termed "lipophobic" had low permeability constants. From the striking correlation between these two variables in a large number of substances, Ross concluded that these relations were in accord with the concepts of cellular membrane structure as originally postulated by Overton. The cell membranes have lipid characteristics; accordingly, the greater the lipid solubility of a metabolite, the more readily does it enter the cell. Ross observed that among all the substances he studied glucose was an exception. It has a relatively low lipid solubility but a relatively high permeability constant. Some other factor must be involved in the ready penetration of glucose into the aqueous humor through the ciliary body and it was natural to suppose that insulin played some role here. Testing this hypothesis experimentally, Ross reported data which are illustrated in Table I.

In the normal rabbit the permeability constant of glucose across the blood-aqueus barrier of the ciliary body was 200 in Ross' units. In the alloxanized preparation, characterized by high blood sugar levels, the permeability constant was approximately 50 per cent of that of the normal. Treatment of the alloxanized diabetic rabbit with insulin restored the permeability constant to normal values. On the basis of these findings Ross concluded that one function of insulin was to influence change in the permeability of the ciliary body to glucose.

Park and his co-workers[8, 9] were the first to obtain direct evidence that the transport of glucose across cell membranes was accelerated by insulin. They used the rat diaphragm, the heart, or the skeletal muscle *in vivo* and *in vitro*. By using isotopic glucose they were able to determine the intracellular free glucose, that is, glucose uncombined with phosphate as a hexose phosphate. Park and his associates showed that

TABLE II—DEPARTURES FROM NORMAL OF THE GLUCOSE METABOLISM OF LIVER SLICES FROM ALLOXANIZED RATS
(Combined data from the literature)

Glucose Uptake	Decreased
Conversion to CO_2	Decreased
Glycogen from Glucose	Markedly Decreased
Glucose Output	Markedly Increased
Glucose From Unknown Sources	Markedly Increased

in the presence of insulin, the concentration of free glucose within the tissue cells was higher than in the absence of insulin. From many experiments of this type, Park and his co-workers concluded: "that an action of insulin on glucose uptake is to accelerate a step concerned with the transport of glucose into the tissues. This step antecedes and is distinct from glucose phosphorylation by the hexokinase reaction."

This so-called transport hypothesis of the action of insulin with respect to glucose in skeletal and cardiac muscle has been amply supported by the work of other authors. However, it cannot be generalized to apply to all other types of tissues, particularly the liver. In fact, as I shall point out subsequently, there is good evidence to indicate the contrary.

Defects of Glucose Metabolism in the Diabetic Liver: The defect of glucose metabolism in the diabetic liver is still subject to considerable divergences of opinion. However, in Table II, I present a summary of metabolic defects of glucose metabolism in the diabetic liver. Much of this evidence has been obtained by the study *in vitro* of liver slices from diabetic rats or cats using isotopic glucose. In summary: The figure shows 1) there is a diminished uptake of glucose; 2) a diminished oxidation of glucose to CO_2; 3) a diminished conversion of glucose to glycogen, hence a diminished glycogen storage; 4) a depression of the ability of the liver to phosphorylate glucose; and 5) a markedly increased new formation of glucose, particularly from unknown precursors presumably protein. One can conclude from this evidence that a metabolic block in the early stages of metabolism of glucose exists in the liver of the diabetic animal. The exact nature of this metabolic block of glucose metabolism in the liver is not completely established. There is evidence that the permeability of liver cells to glucose is not

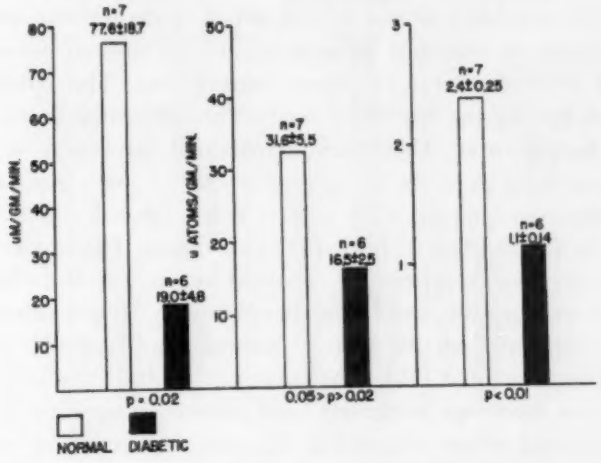

Fig. 2—Oxidative phosphorylation by hepatic mitochondria from normal and diabetic cats. (Data from Vester and Stadie, 1957, ref. 11.)

influenced by insulin. Hence the metabolic block, unlike the case of the muscle, is not concerned with an inhibition of transport of glucose across the cell boundary. A considerable amount of work by Hastings' group[10] at Harvard is compatible with the hypothesis that the defect is concerned with the hexokinase reaction.

Phosphate Metabolism in the Diabetic Animal

It is now well established that the oxidation of certain metabolites by the Krebs' cycle brings about the incorporation of inorganic phosphate into energy-rich types of organic combination, for example, adenosine triphosphate. The reactions involved in the formation of these energy-rich phosphate compounds are collectively grouped under the term "oxidative phosphorylation". The compounds formed become sources of chemical energy for a wide variety of metabolic activities. Much evidence in the literature makes it reasonable to assume that a deficient formation of these energy-rich phosphate bonds may play a role in the metabolic defects of the diabetic animal.

It is fairly well established that oxidative phosphorylation occurs exclusively in the mitochondria. Is this activity of the hepatic mito-

chondria impaired in the diabetic animal? Vester[11] in our laboratory studied the possible existence of this defect in the diabetic animal by measurements of oxidative phosphorylation in isolated mitochondria prepared from the livers of depancreatized cats. The mitochondria were prepared by the customary method of differential centrifugation of liver homogenates. They were equilibrated aerobically in suitable media containing pyruvate as a source of energy and a glucose- hexokinase system to bind the ATP as soon as it is formed.

I show a summation of his data in two figures. Figure 2 compares: 1) oxidative phosphorylation as measured by the rate of formation of adenosine triphosphate, and 2) the phosphorus to oxygen ratio of mitochondria isolated from the livers of normal depancreatized cats. The rate of formation of ATP by the mitochondria from the livers of the diabetic cats (as shown in the left hand column) is significantly diminished compared to that observed in the normal animal. The values are 77 and 19 respectively. In the right hand column are shown the so-called P:O ratios in both instances. The P:O ratio is the ratio between the amount of ATP formed by the mitochondria and the oxygen uptake. This ratio measures the efficacy of oxidative phosphorylation by the mitochondria. When the P:O ratio is zero, for example, the oxidative processes occurring in the mitochondria have not been coupled to reactions converting the low energy adenosine diphosphate to the high energy compound adenosine triphosphate. In other words, the energy of oxidation in the mitochondria has been wasted as heat instead of being stored as adenosine triphosphate for future use. The maximum value expected in the normal animal is of the order of 3.0. In Vester's experiments, the normal mitochondria yielded a mean value of about 2.4 whereas the mitochondria from the diabetic cats gave a significantly lower mean value in the two series of animals of 1.1. Both the ATP values and the P:O ratios indicate the ability of the mitochondria to generate high energy phosphate bonds in the form of adenosine triphosphate is diminished in the diabetic.

Vester also showed that these manifestations of impairment of oxidative phosphorylation in the diabetic cat can be reversed by prior treatment of the diabetic cat with insulin. His experiments were done in the following way. Two or three days after pancreatectomy a liver biopsy was done. Mitochondria were prepared and tested for phosphorylative capacity. Then the cat was vigorously treated with insulin for a period

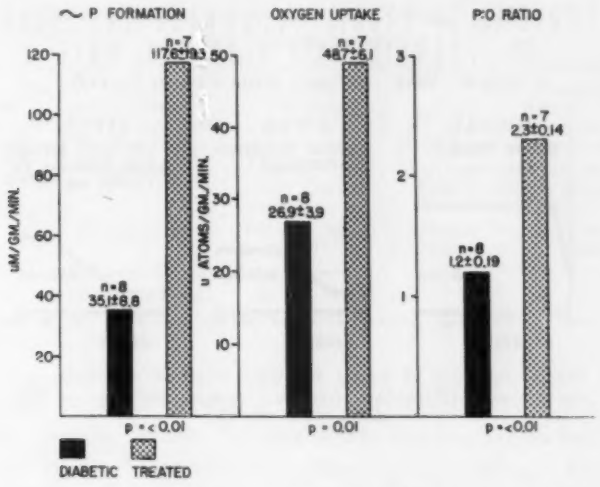

Fig. 3—Restoration to normal of the oxidative phosphorylation by mitochondria prepared from livers of insulin treated depancreatized cats. (Data of Vester and Stadie, 1956.)

of two or three days and restored essentially to normal and a second specimen of liver obtained. As before, mitochondria were prepared and assayed for oxidative phosphorylation. Figure 3 shows the data obtained in a series of eight depancreatized cats.

In the left hand column, the solid column indicates the total oxidative phosphorylation as measured by ATP formation in the diabetic state; the hatched column in the restored state. It is clear that the insulin treatment has restored oxidative phosphorylation in the isolated mitochondria essentially to normal. The P:O ratio which is shown on the right of the slide is also restored to normal.

The summation of Vester's evidence which I have cited here, together with that in the literature, indicates that oxidative phosphorylation is impaired in the diabetic status and this impairment cannot be ignored as a possible factor for departures of both fat and carbohydrate metabolism from normal.

Metabolic Adaptation By Insulin

Recently attention has been focused upon a phenomenon which might be called metabolic adaptation brought about by insulin. By

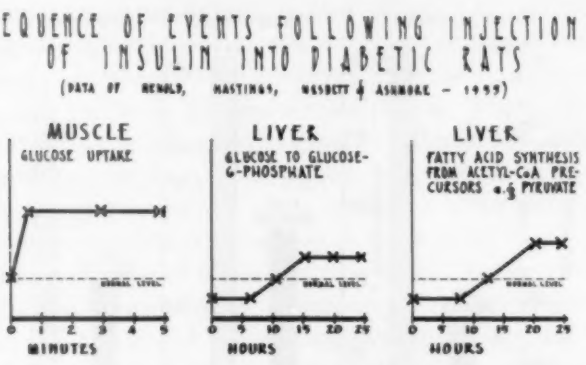

Fig. 4—Sequence of events following injection of insulin into diabetic rats. (Data from Renold, Hastings, Nesbett, and Ashmore, 1955, ref. 12.)

adaptation I mean that in the presence of insulin a change in the function of enzymatic systems of tissues occurs which requires considerable time for full development. This phenomenon has been well summarized by Hastings and his co-workers[12] who studied it at considerable length.

Their results in the case of the diabetic rat are shown in Figure 4. Using the diaphragm as an example of muscle, they showed that the response of injected insulin was immediate. A minute or less after the injection into the intact rat the animal was sacrificed and the diaphragm rapidly removed. In this brief time, the diphragm had responded to the insulin as shown by the fact that when it was equilibrated *in vitro* in a medium containing glucose, it showed a significant increase of glucose uptake and glycogen synthesis compared to control series of diaphragms obtained from rats without prior insulin injection. Liver slices obtained from the same rats responded to the injected insulin so slowly that treatment periods of 6 to 24 hours were required for full restoration to the normal from the diabetic status. As measures of response to insulin, Hastings quoted among other effects the total phosphorylation of glucose, the incorporation of fructose, pyruvate, or acetate into higher fatty acids. The responses in the case of the liver are strikingly different from those of the muscle. Insulin reaction in the diaphragm is essentially instantaneous and appears to be concerned with the transport of glucose. In contrast, insulin action in the liver is slow and in the diabetic can only be demonstrated by injection into the intact animal. A reasonable hypo-

TABLE III—UNIFIED CONCEPT OF INSULIN ACTION
(Data from Stadie—1956)

Tissue	*Mechanism of Action*	*Site of Action*	*Chief Metabolic Effects*
Muscle	Combination	Cell Surfaces	Glucose Transport et seq.
Liver	Adaptation	Enzyme Systems: Contra Pituitary	Glucose Oxidation, etc.; Fatty Acid Synthesis; Oxidative Phosphorylation (?)
Adipose	Adaptation	Enzyme Systems	Glucose Oxidation, etc.; Fatty Acid Synthesis
Brain	*No Demonstrable Action*		
Other	*Insufficient Data*		

thesis would be to assume that by some mechanism which at present is not known, insulin permits the liver slowly to complete an enzyme system which in the absence of insulin has lost its function in whole or in part. The adaptation requires perhaps synthesis of new proteins or the formation of co-factors. These reactions take time and further suggest the possibility of diverse types of insulin action in the liver affecting glucose or fatty acid metabolism.

On the basis of these considerations, it is possible to formulate, as a working hypothesis, what might be called a unified concept of insulin action. I show this in Table III. Four columns are considered: 1) tissue; 2) mechanism of action; 3) site of action; and 4) chief metabolic effects. In muscle, the mechanism of action may be considered to be a combination of insulin with the muscle and the site of the action perhaps upon cell surfaces. The main metabolic effects would be an increase of glucose transport into the cell which of course would accelerate phosphorylation and therefore further reactions.

In the liver, adaptation is necessary, time is required, the enzyme systems are under the contra-control of pituitary factors, and the chief metabolic reactions involved are glucose oxidation, fatty acid synthesis, oxidative phosphorylation and perhaps others. In adipose tissue, the situation is about the same as that outlined for the liver. In the brain, as many experimenters have found, there is no demonstrable action of insulin. In other tissues the data available are insufficient to make discussion profitable. This unified concept of insulin action need not be complete nor even free of errors so long as it has some meaning to the experimenter and is provocative of further experimentation,

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FAT METABOLISM IN DIABETES*

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THE known disturbances of fat metabolism in diabetes fall into three categories: impairment of fatty acid synthesis, increased mobilization of fat from tissue stores, and abnormal accumulation of lipid in various tissues. The first is evidenced clinically by progressive emaciation of severe untreated diabetics; the second, by variable elevation of plasma lipids, especially triglycerides; and the third by obesity, atherosclerosis, fatty liver and the like which, though not limited to diabetics, do associate with the disease strongly enough to suggest a common etiology.

At the present time the impairment of fatty acid synthesis and its relation to carbohydrate metabolism can be interpreted in some detail, thanks to the remarkable advances in fat chemistry during the past decade. Knowledge of the transport processes—the controlled flow of lipids from one organ to another, and adjustment of depots to the need of consumer cells—has advanced less rapidly, so that interpretation of the elevated lipid concentrations must rest on indirect evidence and conjecture. As to the third category, the degenerative diseases, there exists a vast incoherent literature that leaves the fundamental causes as mysterious as ever.

A reduction of fatty acid synthesis, similar to that encountered in diabetes, appears after a few hours of starvation and is reversed by feeding a relatively small amount of carbohydrate.[1] So far as is known at present, the diminished synthesis of fat in diabetes is simply an exaggeration of this normal response to lack of carbohydrate. The diabetic fails to utilize glucose and so exhibits symptoms of carbohydrate deficiency. Since the functional deficiency imposed by a cellular block is far more severe than one due only to lack of dietary carbohydrate with some internal sources remaining, it is not surprising that the adaptation of fat metabolism in diabetes requires more extreme changes and evokes more marked symptoms.

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Liver slices taken from either fasting or diabetic animals show very little synthesis of fatty acid from labelled glucose or acetate, whereas slices from livers of animals pretreated with glucose or insulin synthesize fat at an impressive rate.[2] In general, the manufacture of fatty acid by tissue slice (liver or mammary gland), by homogenate or by systems of soluble enzymes with acetate as a substrate requires a simultaneous oxidation of citrate or some equivalent component of the tricarboxylic cycle.[3] The coupling between oxidation and synthesis appears to be quite specific for fatty acids, since the formation of cholesterol from acetate proceeds at a normal or accelerated rate in slices of diabetic liver.[4]

The nature of the coupling has been revealed by work published in the past few months.[5] Acetyl-CoA readily condenses to acetoacetyl-CoA in the diabetic liver and is reduced to the 4-carbon unsaturated fragment, crotonyl-CoA. Further reduction to butyryl-CoA requires a strong reducing agent, possibly triphosphopyridine nucleotide which is hydrogenated by a coupled oxidation of iso-citrate. The block to synthesis of long chain fatty acid in liver slices appears to involve only this step, since further extension of butyryl-CoA proceeds at a normal rate in slices from diabetic rats. Other impediments to lipogenesis in clinical diabetes might also be of importance, but this block at the 4-carbon step appears to be limiting in the experimental material so far studied, and most likely is dominant in clinical disease. If such a block did develop, obviously it would contribute to the accumulation of ketone bodies.

Another process governing fat metabolism is the metabolically-controlled deposit and mobilization of fatty acids in adipose tissue. *In vitro*, the uptake of labelled stearic acid from serum into triglycerides of mesenteric fat is depressed if the animal is fasted in advance and enhanced if it has been fed. There is more than physical exchange involved in this since M/500 cyanide abolishes the uptake.[6] In the intact normal organism a feeding of glucose causes reduction of total serum fat, and if given after a fatty meal, diminishes the amplitude of alimentary lipemia.[7]

It seems likely that the control of plasma non-esterified fatty acids (NEFA) by this or a related mechanism is of importance in regulating the flow of fat from depots to liver and other tissues.[8] The NEFA fraction, although low in concentration, turns over with exceptional

velocity (half time about 2 minutes),[9] and so transports a quantity of fat comparable in magnitude to the total caloric expenditure. A few minutes after injection of albumin-bound C^{14} palmitate, the label is distributed widely throughout body tissues. A part—more or less depending on the fasting or fed state of the animal—appears in respiratory CO_2, and a part is esterified into tissue lipids, especially triglyceride and phospholipid of the liver.[10] In some organs, oxidation of NEFA can account for the major part of energy metabolism; comparison of NEFA and oxygen concentrations in blood from arteries and coronary sinus showed that the uptake of NEFA by heart muscle was practically equivalent to the amount of oxygen consumed.[11]

In diabetic ketosis the concentration of NEFA is increased two or three fold.[12, 13] If a labile diabetic fails to receive his morning dose of insulin the NEFA level in his plasma rises sharply, preceding the appearance of ketonemia or ketonuria. After ketosis is developed, treatment with adequate doses of insulin causes a prompt fall of NEFA, paralleling the fall of glucose and anticipating by some hours the disappearance of ketone bodies from urine. Even when apparently in good clinical control, diabetic patients tend to have an elevated concentration of NEFA in fasting plasma and a comparatively weak fall in NEFA concentration in response to administration of glucose or glucagon.[13]

Quite probably the flow of fatty acids from blood into liver and other tissues is increased when the concentration of NEFA rises above normal levels. Evidence on this crucial point is, however, indirect. In normal dogs insulin appears to reduce the input of fatty acids from tissue stores to plasma but to have no effect on the outflow of labelled palmitate from plasma to tissue.[14] In normal human subjects insulin plus glucose abolished the arteriovenous increment of NEFA in saphenous vein, which drains fatty tissue—and so presumably reduced NEFA level by control of mobilization.[11]

If this inference is confirmed, it might bear on the cause of ketosis, for the development of severe ketonemia probably requires an accelerated transfer of fatty acids from depots to liver tissue. The maximal output of ketone bodies from the liver of a diabetic cat, equivalent to about 2.3 gm. fat per kg. body weight per day,[15] is greater than the total turnover of neutral fat in the normal liver (which, as judged from a half time of about 3.5 hours in dogs[16] and a total quantity of about 0.3 gm. neutral fat in liver per kg. body weight[17] amounts to about 1.5

gm. fat per kg. day). In human subjects the peripheral tissues apparently can oxidize ketone bodies at a rate equivalent to about 2.5 gm. fat per kg. body wt. per day without the appearance of ketosis.[15] Therefore, a simple blockage of synthesis, without reduction in the rate of hepatic oxidation or increase in the amount of substrate delivered, would not seem likely to throw the diabetic patient into coma.

It has been suggested that the pathway for oxidation of acetate might be blocked by deficiency of oxalacetate, which joins with acetyl fragments to form citrate.[18] That such a block, if it existed, would be ketogenic is indicated by the production of acetoacetate in liver slices poisoned with malonate. But there is no evidence that the quantity of oxalacetate is reduced to this extent in ketosis. On the contrary, the undiminished or increased consumption of oxygen by ketotic patients argues for a normal supply of this essential component of oxidative metabolism.[18]

However, the quantity of oxalacetate probably becomes relatively deficient in comparison with acetyl if an intemperate discharge of NEFA from depots loads the liver with fatty acid substrate, and a block in fatty acid synthesis traps the material into a swollen pool of active acetate. Under these conditions acetoacetate certainly would be produced in excess quantity, and other unblocked synthetic processes, such as the manufacture of cholesterol from acetyl fragments,[4] might be driven to greater production. Even without an impediment to fatty acid synthesis, a normal liver responds with a five fold increase in ketone body production when loaded by an infusion of octanoate.[19]

It is of interest to consider the possibility that excess mobilization of fatty acid might also contribute to the production of chronic accumulative lesions: fatty liver, xanthomata, and various kinds of arteriosclerosis. Direct evidence is lacking, but the high incidence of these complications in diabetic patients giving a history of poor control and repeated ketosis supports the idea.[20] At any rate, the meaning of the clinical expression "control of diabetes" is becoming more refined and specific. No longer should we regard freedom from manifest symptoms as evidence of successful therapy, when abnormalities in lipid synthesis and transport can be demonstrated. Whether the NEFA level or some other index of transport will prove to be practically useful remains to be tested. Until some such index is developed and used, it is unlikely that the long term prognosis of diabetes can be improved.

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RADICAL PERINEAL PROSTATECTOMY FOR EARLY CANCER*

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DURING the last decade a large segment of the medical profession has shown a rapidly growing interest in the feasibility of eradication of prostatic cancer by radical surgery. There are probably numerous reasons for the development of this interest, but five in particular come to mind. These are: an increased prevalence of the disease; a rising death rate; the failure of long-term control by endocrine therapy; the availability of the retropubic procedure; and the favorable results of radical perineal prostatectomy in selected cases.

Statistics obtained from postmortem examinations indicate that prostatic cancer is present in at least 14 per cent of men over 50 years of age.[1] In addition to this previously established fact, the Public Health Service reported in 1952 that it had become the second most prevalent malignancy in the male, exceeding in prevalence that of all organs except that of the skin. Moreover, its incidence was found to have increased 38 per cent between 1938 and 1948.[2]

The Public Health Service also reported in 1952 that of all men who died of malignant disease in the geographical area surveyed, 15.9 per cent died of prostatic cancer. This figure was exceeded only by the percentage of patients dying with cancer of the stomach and lung.[2]

Endocrine control of prostatic cancer has been only temporary in the overwhelming majority of histologically proved cases. Nesbit and Baum[3] (1950) reported the results of castration-estrogen therapy based on figures furnished them by 15 urological clinics in this country. Of 263 patients with metastases on admission, 20 per cent lived five years after castration-estrogen therapy, as compared with 6 per cent of 231 untreated patients. Of 324 patients without metastases, 44 per cent lived five years after castration-estrogen treatment, as compared with 10

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per cent of 273 untreated controls. Staubitz, Oberkircher and Lent[4] (1954) found that 16 per cent of their patients with metastases, and 24 per cent of those without metastases, lived ten years after endocrine treatment.

Since 1951 some 200 or more patients, who relapsed after castration-estrogen therapy, have been subjected to bilateral adrenalectomy. The results in these cases have been reported in the literature. Although some of these patients unquestionably obtained marked subjective relief, often with disappearance of pain, objective improvement has not been striking. Rarely has there been a decrease in the size and consistency of the local mass or in the palpable soft tissue metastases. Bony metastases have remained essentially unchanged in the roentgenograms, and for the most part, length of life has not been prolonged.

The relatively recent development of a surgical avenue to the prostate far removed from the regrettably unfamiliar perineal route has been responsible for stimulating a large number of urologists, here and abroad, to advocate and perform total prostatectomy for cancer.

Finally, the published results of radical perineal prostatectomy leave little doubt concerning its value, even though its applicability is somewhat limited. Approximately 10 per cent of patients with cancer of the prostate examined at the Johns Hopkins Hospital over a period of 50 years have been subjected to this procedure. During the last ten years the figure for operability has increased from 10 per cent to 19 per cent, despite the fact that the criteria governing suitability have recently been more rigidly defined. The malignant process must be grossly confined to the prostate. This means that the fibrous sheath or true capsule is perfectly smooth, and the gland is movable. The seminal vesicles are normal on palpation throughout their entire extent with no induration along their outer sides or between them. The membranous urethra and bladder neck, and roentgenograms of the spine, pelvis and upper femurs are all normal, together with the level of the serum acid phosphatase. Furthermore, the patient otherwise should have a life expectancy of approximately ten years. For this reason few patients over 70 years of age are suitable subjects.

Characteristically, the earliest stage of prostatic cancer that is recognizable by digital rectal palpation is a small nodule usually quite firm and incompressible in the periphery of the gland and close to the examining finger. It has been stated that only about 5 per cent of

patients with prostatic cancer throughout the country are seen in such an early stage of their disease. This is because a rectal examination, unfortunately, is rarely made by the family physician unless the patient is having specific symptoms, at which time he is usually no longer a suitable subject for radical prostatectomy. It seems obvious that this situation can and should be corrected. In the Army where routine annual rectal examinations are mandatory in men over 40, early, operable prostatic cancer has been detected in 54.5 per cent.[5] A better understanding of the problem by general practitioners should eventually result in a much higher figure for operability than now exists.

The operation devised by the late Dr. Hugh Young[6] in 1904 consisted of the surgical removal of the entire prostate gland, the bladder neck, and the seminal vesicles with their anterior and posterior fascial coverings in one intact specimen, by way of the perineum. Kahler[7] has shown that only about 16 per cent of localized tumors arise within areas of nodular hyperplasia. The rest arise in the peripheral portion of the gland, or surgical capsule. Therefore it is rare for an early cancer to be completely removed by enucleation, or by transurethral resection of the hyperplastic mass, for the portion commencing in, or invading, the surgical capsule is left behind after these operations.

Young's original operation, with a few minor modifications, is still used today and 401 have been performed at the Johns Hopkins Hospital. Approximately half of these have been done in the last ten years, since alert practitioners are now making the diagnosis in a much earlier stage.

Up to 1944, 127 patients with histologically identified cancer survived the operation and have been followed.[8] Of these, 48 had advanced cancer with grossly palpable involvement of the fibrous capsule of the gland or the seminal vesicles. These patients were operated upon before the era of endocrine therapy, which began in 1941, in the hope that some might be salvaged. Surprisingly enough, six of the 48 (12.5 per cent) did live ten years, and only two later on received endocrine assistance. There were 79 cases in which the preoperative rectal examination showed no palpable evidence of extension beyond the prostate. Thirty-seven per cent of these patients lived ten years without evidence of recurrence. However, microscopic examination of all these surgical specimens showed that the seminal vesicles actually were involved in 39 cases, or practically one-half of the group. Of the remaining 40 cases

TABLE I—CANCER MICROSCOPICALLY CONFINED TO PROSTATE, 40 CASES

	Lived 10 Years or Longer Without Cancer and Without Endocrine Support	*Died With Cancer*	*Died Without Evidence of Cancer*
Grade 1	13	2	1 year, 1 2 years, 3
Grade 2	4	2	3 years, 2 5 years, 1
Grade 3	0	1	6 years, 1 7 years, 3
Not graded	4	2	9 years, 1
Total Cases	21	7	12

of proved cancer, there was no microscopic evidence of extension beyond the prostate. Twenty-one (52 per cent) of these patients lived ten years or longer without recurrence or metastasis and without endocrine treatment (Table I). The surgical specimens removed from the 21 patients who lived ten years or longer without cancer and those from the seven who died with cancer have been carefully scrutinized by Dr. Frederick G. Germuth, Jr., of the Department of Pathology. Of the 21 patients who lived, perineural lymphatic involvement was seen in 12 cases. In nine of these the tumor was considered Grade 1, and in three, Grade 2. Of the seven patients who died with cancer, the perineural lymphatics were found involved in four of the five that were graded.

Dr. Germuth prefers the use of three grades of malignancy instead of four. For this reason, tumors of Grade 1 seemed to predominate. He states: "The tumors were divided according to their microscopic appearance into three different grades of malignancy, the least malignant being Grade 1, and the most malignant Grade 3. The factors observed in grading were: the degree of differentiation; the character of the cells and nuclei; and the completeness with which the normal gland structure was reproduced. Grade 1 consisted of tumors showing well developed acini lined by cuboidal cells. In some instances, slight cellular atypicalities were present. (In the Broders classification some of these tumors would have been designated as Grade 2.) Grade 2 consisted of tumors showing foci of incomplete acinar formation, such that solid cores of tumor were frequent. Grade 3 consisted of tumors demonstrating almost complete lack of acinar formation; for the most part, the microscopic

sections showed scattered undifferentiated cells in random arrangement throughout the stroma."

The average age of patients who lived ten years or more without recurrence or metastasis was 62.8 years, and the youngest patient in this group was 54 years old at the time of operation. Of the 13 patients with tumors of Grade 1, the average age was 61, and of those who had tumors of Grade 2, it was 65.7 years.

There were nine patients (23 per cent) who lived 10½ to 17 years after operation whose seminal vesicles, though grossly normal, were found to be involved after careful microscopic study. Five patients with Grade 1 tumors and one with a Grade 3 tumor have had no recurrence or metastasis, the latter patient having lived 14 years. One patient with a Grade 1 tumor was apparently well for 12 years but died with cancer 16 years after operation. Another with a Grade 2 tumor was clinically free of cancer 11 years after operation but died with cancer six years later, or 17 years after operation. Perineural lymphatics were involved in both cases. One additional patient with an ungraded tumor was clinically well for nine years but died with cancer two years later. Therefore nine of 39 patients with microscopic, but not gross, involvement of the seminal vesicles lived ten years or longer, and six of these 39 patients (15 per cent) have remained free of cancer without endocrine assistance.

These figures show that involvement of the seminal vesicles reduces considerably the ten-year survival rate after radical prostatectomy, and that the cancer is histologically confined to the prostate in only about half the cases in which the vesicles seem normal on rectal examination. Although tumors in the lower grades of malignancy are definitely lethal, their somewhat slower growth and spread probably account for the fact that they so often produce lumps or nodules that can be felt. Tumors of high grade malignancy are seldom recognized in early stages, probably because of their much faster rate of infiltration. Turner and Belt[9] report that more than 78 per cent of their 229 cases treated by radical perineal prostatectomy consisted of tumors of Grades 1 and 2, and only 3.6 per cent of Grade 4. Culp[10] also states that in 67 radical perineal prostatectomies done by him at the Mayo Clinic, 63 tumors were graded 1 or 2, and none was graded 4. Seventy per cent of his patients who could be followed five years were free of tumor. Three recurrences were among tumors graded 1, two recurrences among

those of Grade 2, and one recurrence among his small group of four Grade 3 tumors. Turner and Belt[9] found that eight of 17 patients with cancer microscopically confined to the prostate lived ten years or longer (47 per cent).

It is difficult to obtain data permitting an accurate comparison of the results of radical perineal prostatectomy with those after palliative treatment of patients with histologically proved cancer in similar stages of development. However, Barnes[11] selected 31 patients who he believed were suitable subjects for the radical operation, but instead of operating he gave them endocrine therapy. Twenty-two per cent of these patients were alive at the end of ten years, still with cancer. Therefore, from the rather limited number of available cases permitting a long-term survey it seems that the radical operation in suitable cases provides a survival rate far superior to that afforded by hormones. The questions that remain to be answered concern the risk of operation and the possibility of incontinence and other complications.

Impotence usually follows effective endocrine therapy as well as radical prostatectomy, and therefore may be disregarded. A distressing, and avoidable, situation, however, is that of permanent impotence resulting from the endocrine treatment of a patient whose prostatic nodule was not cancer. Of 211 prostatic nodules clinically compatible with cancer, which were studied microscopically at the Johns Hopkins Hospital, 108 were benign and 103 were malignant.[12] A surgeon who castrates or renders impotent by estrogen a patient who has a benign area of induration in the prostate gland may be subject to a lawsuit.

It is impossible to distinguish a localized benign nodule in the prostate from one that is malignant by palpation alone. If the roentgenogram shows that the nodule is not a calculus the diagnosis will depend on accurate biopsy. This should be practically 100 per cent accurate when properly taken through a perineal approach. If the tissue is benign the patient is out of the hospital in a few days, with peace of mind, without sacrificing his sexual function, and without submitting to endocrine treatment for the rest of his life.

The mortality and morbidity following radical perineal prostatectomy have steadily declined through the years. In the last 200 cases at the Johns Hopkins Hospital there were six deaths, but there has been no postoperative death on the private service in more than 13 years. Of the last 100 cases, 65 patients were discharged from the hospital between

11 and 19 days after operation.

In these last 100 cases there have been no disabling consequences. Temporary stricture of moderate degree developed at the site of vesicourethral anastomosis in 15 per cent. Thrombophlebitis of the veins of one leg occurred for a time in six cases. The rectum was injured in four cases, but complete healing followed in all. There have been no fistulas. Perfect urinary control was established in a short time in 84 to 95 per cent of the cases, depending on the type of closure used. With the posterior figure-of-eight mattress suture there was no permanent incontinence in 30 cases.

Conclusions

Cure of prostatic cancer can be accomplished only by early, complete surgical extirpation. This is feasible in men who have a life expectancy of ten years and who show no evidence of metastasis or of gross extension of the cancer beyond the prostate gland itself. In about half of these cases the tumor will be microscopically localized to the prostate. Fifty per cent of these patients will survive ten years free of cancer after radical perineal prostatectomy, as compared with the expected survivorship of 53 per cent for men of the same age group in the general population.

At the present time these criteria for operability are satisfied in only a small percentage of cases. This percentage could be greatly increased if a presumptive diagnosis of the disease were made more often in the nodule stage by an annual one-minute examination by the family physician.

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THYROID DISEASES IN CHILDREN AND ADULTS

*Transcription of a Panel Meeting**

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* Presented at a combined meeting of the Sections on Medicine, Pediatrics, and Surgery with the Stated Meeting of The New York Academy of Medicine, November 1, 1956.

MODERATOR SIDNEY C. WERNER: It is evident from the nature of the subject that the discussion this evening will not be entirely definitive. Rather, it will be a presentation of current opinion, or at least opinion of members of the panel, on various aspects of thyroid disease.

We are fortunate in having a group of men who are competent in every aspect of their specialties, particularly as related to thyroid disease.

To begin the presentations, and since the other panelists will speak about various therapeutic aspects of thyroid disease, I thought it might be timely and useful to discuss a bit the current status of diagnostic procedures in hypo- and hyperthyroidism.

I believe most physicians, if they had a choice among the various types of tests, would currently select two procedures, one using radioactive iodine and another using the chemical determination of the level of circulating thyroid hormone. However, these two tests are not foolproof and have certain limitations which make the use of the basal metabolic rate and fasting cholesterol still worth while. I plan, therefore, to outline the factors which tend to limit or invalidate the use of radioactive iodine and chemical procedures.

If one employs radioactive iodine, one can use the standard 24 hour uptake, which we introduced some years ago. We pointed out at that time that there was about 85 per cent correspondence with the correct diagnosis.

Recently, Keating and his associates at the Mayo Clinic have felt that one can increase the accuracy of the method by settling for a six-hour determination; nevertheless their results do not achieve much more than 90 per cent correspondence with the final diagnosis.

Since renal difficulties and cardiac difficulties may create trouble with all radioactive uptake procedures, these in turn may affect the accuracy of the diagnosis. The thyroid clearance, which was proposed early by Pochin and later modified by Berson and others, is a method of approach to correct these factors. Dr. Pochin and his group also proposed a method comparing the quantity of I^{131} collected in several hours' time by the thyroid with the quantity in the thigh. They found that in hyperthyroidism much more was collected by the thyroid and correspondingly much less by the tissues. This method depends on the rate of uptake of I^{131} and the results correlate well with those from clearance studies.

Other investigators have considered the release by the thyroid of the final products of hormonal synthesis and thereby determine the conversion ratio between organic and inorganic serum I^{131} at 24 hours or rely on the 48 or 72 hour determination of the serum precipitable I^{131}.

No matter what method is used, however, certain substances cause confusion. For example, a patient taking iodides in medicinal form, often not knowing that iodine is being taken or in using large quantities of iodized salt, has an uptake of I^{131} which will obviously be less because of the saturation of the gland by the iodide excess. Also, the use of organic iodinated compounds, such as for a gallbladder x-ray series, etc., may liberate large amounts of iodide upon metabolism within the body and thus lower uptake, often for weeks or months. If a patient is taking thyroid, for example, I^{131} uptake may be inhibited to levels suggestive of hypothyroidism. Cortisone also may inhibit uptake.

Contrariwise, as Dr. Stanbury's later discussion will indicate, in certain examples of non-toxic diffuse goiter there may be an extremely high uptake and yet the patient may not be hyperthyroid. This is due to the fact that the gland is pouring out incomplete products of thyroid hormone synthesis and not thyroxine. Thus there is a high turnover of iodine but no excess of thyroid hormone. In nodular goiter the uptake may be falsely low in some patients with hyperthyroidism, and falsely high in others who are overtly hypothyroid.

Iodine want is another instance in which uptake is elevated, because the gland adapts itself to lack of iodine by taking up much more efficiently what iodine is available to maintain euthyroidism.

I have mentioned renal and cardiac disease where the thyroid clearance is useful but not the uptake method. In cirrhosis of the liver uptake may be elevated; and of course in pregnancy and lactation the use of I^{131} is unjustified.

The level of chemical protein bound iodine (PBI) is equally invalid diagnostically under certain circumstances. In pregnancy there is a physiological increase in the circulating level, as Dr. Peters pointed out, so that one cannot be sure of a diagnosis of hyperthyroidism made on this basis. In infancy, also, there is a physiological rise in level. Again, iodides by mouth may bind to albumen and be determined with organic iodine. Although butyl extraction will eliminate the iodide error, it does not avoid the increases caused by the circulating iodinated dyes.

Treatment with thyroid, as I have mentioned, may cause changes in level of PBI, especially if triiodothyronine is used. The serum precipitable iodine in a patient given this latter compound therapeutically does not rise. The hypothyroid patient may be made euthyroid, go to another doctor who determines the serum iodine and finds no circulating hormone by this test, and may then receive more thyroid. Also, the hyperthyroid status of the patient taking excesses of triiodothyronine by mistake or design will not be revealed by the PBI method.

Finally, the method is tricky and one should be cautious in the interpretation of results especially from an unfamiliar laboratory. I think in this situation the determination of the basal metabolic rate should be done and is helpful under the circumstances which I have listed above. Also, after the treatment of hyperthyroidism with I^{131}, other indices may often be temporarily unreliable yet the BMR may be found to be quite valuable. In this regard, the cholesterol determination in the diagnosis of hypothyroidism, or in following the progress from hyper- to euthyroidism after treatment, may also be very useful.

Now I should like to ask Dr. Elliott if he would discuss the subject assigned to him, *Current Surgical Concepts of the Treatment of Thyroid Cancer.*

DR. ROBERT H. ELLIOTT: What I propose to do in a very brief period of time this evening is to go over with you some of the problems which surgeons face in certain of the current concepts of the treatment of thyroid cancer.

In some areas in the field of thyroid cancer therapy so much confusion exists that almost irrespective of the opinion one ventures, one can find eminent authorities who are in agreement and other authorities equally well qualified who are in disagreement.

Perhaps it might be better to start with the agreements rather than the disagreements. We find, for example, that pathologists in the larger institutions are, for the most part, fairly well agreed on the three different histopathological grades of cancer, Grade I being the least malignant and the best differentiated; Grade III being the most malignant and the least differentiated; and Grade II being an in-between group.

It is fortunate for the human race that Grade III cancer is not any more common than it is. It occurs in about 11 per cent of most series. As you doubtless all know, it is almost invariably fatal. It is

distributed equally between the sexes. It is uncommon before the age of 50 and, unfortunately, by the time it is seen by the surgeon it is usually inoperable. Frequently, the most he can do is a tracheostomy with or without removal of some of the bulk of the tumor in order to help relieve obstruction. Sometimes the advisability of performing even this operation may be debatable, for cutting into the tumor may spread it or cause it to grow out of the wound. Thus surgery may sometimes do more harm than good. I think all will agree that this is an unfortunate group.

It is in the surgical management of the two less malignant groups, I and II, that most of our confusion exists. There are various schools of thought as to how they should be treated. One school believes that one should do no more than remove all visible cancer in the neck. At the opposite end of the scale is the group which believes that a total thyroidectomy with radical neck dissection should be done. Under most circumstances the reasoning on this score parallels that which dictates a radical mastectomy with axillary dissection for carcinoma of the breast. However, it should be pointed out that in most instances Grades I and II carcinoma of the thyroid are not comparable to the average carcinoma of the breast from the point of view of malignancy. This of course is what has led to our dilemma, for Grade I carcinomas are the commonest, comprising approximately 50 per cent or more in the various published series, and these carcinomas may be quite benign indeed. We have two patients who, we feel reasonably certain, may have had Grade I carcinoma for as long as 50 years in one instance and 55 years in the other. Many of these patients die of causes entirely unrelated to their relatively benign form of thyroid cancer. Therefore it is frequently hard to determine which thyroid cancers are going to do away with the host progressively and which ones are not.

We have adopted the following policy at Presbyterian Hospital: We are agreed, as I think almost all thyroid surgeons now are, that when the solitary thyroid nodule is encountered, the minimum surgical procedure should be a lobectomy with removal of the isthmus. It is also our present policy to do a total thyroidectomy if a positive diagnosis of cancer can be established at operation by frozen section. We may even do the latter procedure if the frozen section is equivocal and the gross pathology is highly suspicious, because we know that frequently frozen section diagnosis cannot be too accurate. In addition to removing

the entire thyroid gland, we perform at the same time what we call a paraglandular dissection, which includes the removal of the superior and inferior isthmic lymph node bearing tissue, the lymphatic chains parallel with the gland along with the jugular veins, and probably most important, the chains along the recurrent nerves down behind the gland. This material is then submitted for examination and we decide what, if anything, need further be done, depending upon what the pathologists tell us concerning the disposition of the cancer in the nodes. If there is no cancer in the nodes, we usually stop there and do no more. On the other hand, if the nodes are extensively involved, we proceed to do a radical neck dissection on one or both sides, either staggering these procedures, or doing a total thyroidectomy and a one-sided neck dissection all at one time. We believe that total thyroidectomy with paraglandular dissection is a very important step. It sets the stage for any future necessary surgical therapy. It clears the gland area so that in subsequent procedures we do not have to repeat the rather delicate dissections along the recurrent nerves.

Now having said that, I would like to leave you with what I think is one of the surgeon's most vexatious problems at the moment and that is the non-toxic nodular goiter in which a small cancer is found in the permanent sections after the patient has gone home or at the earliest after the patient has left the operating room. What ought we to do when that occurs? Should we bring the patient back and do a total thyroidectomy on him, if we have not already done so? What, if any, additional therapy is indicated? I hope we may have occasion to discuss this problem a little later.

I trust that I have not further confused an already confusing situation and I hope that what I have said may stimulate you to ask some questions subsequently.

MODERATOR WERNER: Thank you, Dr. Elliott.

Dr. Stanbury will change from the subject of cancer to the subject of *Non-toxic Goiter*.

DR. JOHN B. STANBURY: In our laboratory in Boston we have been chipping away at the problem of nodular goiter of various sorts for the past seven years and I wish I could report that many chips have flown but I cannot. We have found it a vexing problem. However, I do think we have some insight in a small segment of the problem and I would now like to show you examples of this.

Figure 1.—16-year-old female with cretinism and goiter.

Figure 1 shows a patient of 16 years who came to us in 1949. She was of particular interest because she had a huge goiter in her neck. Also, she was a cretin. The most interesting thing of all was that she had three siblings who were just like her. We have had all four of them to study. I shall not go into the details of the observations that were made but I would like to say that we think we have shown in this patient and in her sibs., that the problem is that although this patient is quite capable of taking up plenty of iodide she cannot do anything with it. The iodide simply remains for a short time in the thyroid gland.

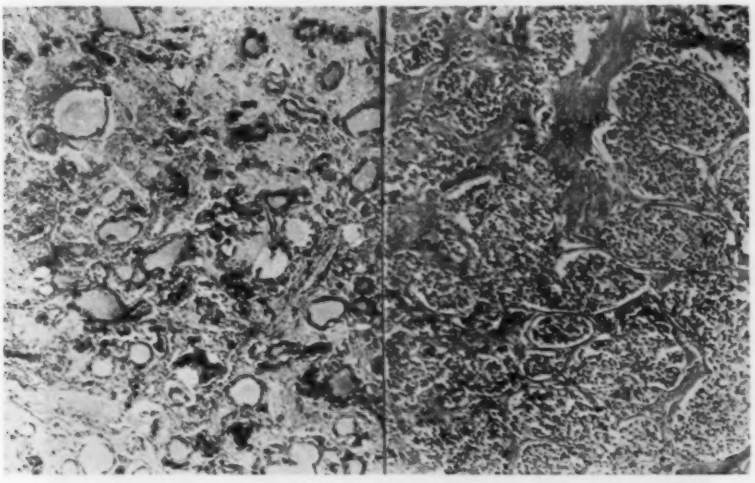

Figure 2.—Histological pattern observed in the gland of the subject of Figure 1. Note the hyperplasia and replacement fibrosis.

never becomes fixed into the hormone precursors, and in time is excreted by the kidney. All the studies we have done in the patient over the subsequent years confirm this point of view, so that we visualize this patient as having a defect at the stage in hormone synthesis where iodide is fixed onto tyrosyl groups. This perhaps is an oxidative step in the thyroid gland.

Figure 2 is a picture of her gland at surgery to show the intense hyperplasia and distortion of cellular pattern which was found in this extremely active thyroid gland.

The next patient represents a different problem. She also had a nodular goiter for a long time, and was an incomplete cretin. She had a sister who was just like herself. Again these studies have extended over a fairly long period of time. I won't go into detail but the studies seem to add up to a different defect. This is that she cannot couple mono- and diiodotyrosine into triiodothyronine and thyroxine. There is a block at this enzymatic step in hormone synthesis. Accordingly, not being able to effect this step, she remains hypothyroid and with the attendant defects.

Figure 3.—26-year-old male with congenital hypothyroidism and goiter which was noted at birth.

More recently, while working with Drs. Kassenaar, Meijer and Querido in Holland, this patient was studied (Figure 3). He was a large chap with a nodular goiter, evidence of retardation of growth in the past and hypothyroidism, evidenced by a very low serum protein bound iodine concentration. He had a brother who was a cretin and who also had a large nodular goiter.

We had one other cretin who has an identical defect. Perhaps the most interesting thing about this third patient was that she had a

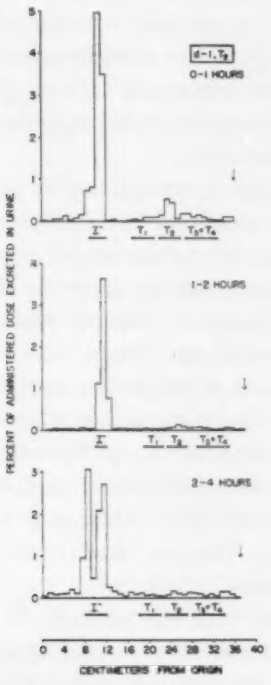

Figure 4.—The metabolism of intravenously administered diiodotyrosine in a normal patient. The bars on the abscissa indicate the positions taken by the indicated carriers. I^-, iodide; T_1, monoiodotyrosine; T_2, diiodotyrosine; T_3 and T_4, triiodothyronine and thyroxine, respectively. The chromatograms were run in the butanol-acetic acid system.

mother, sister and three aunts, all of whom were normal except for the fact that they had large thyroid glands. These patients all seem to share in the same type of metabolic defect. In the blood of these cretins after radioactive iodine there was mono- and diiodotyrosine present in large amounts. This is not found normally in the blood. When these patients were injected with diiodotyrosine a rather unusual result occurred.

Figure 4 shows what happens when one injects diiodotyrosine labeled with radioactive iodine into a normal individual. This is the urine

pattern. You will note that in these scans from chromatograms, all the radioactivity is present in the spot corresponding to iodide. Nothing appears elsewhere except at the diiodotyrosine spot. When the cretin and his brother and the other patient were given diiodotyrosine, an identical pattern was observed except that all the activity, quantitatively, was at the diiodotyrosine spot.

In the normal process of mobilization of the thyroglobulin, mono- and diiodotyrosine are mobilized but don't escape from the gland. It seems therefore that the defect here might be that these patients could not deiodinate mono- and diiodotyrosine in the normal fashion. We have formulated this group of patients who are cretins with hypothyroidism because they lack the capacity to remove iodide from mono- and diiodotyrosine. This is so not only in the thyroid gland but systemically as well. One further point is that we were able to demonstrate this defect in thyroid tissue of one of the cretins in the Warburg apparatus. These patients are numerically small in the general problem of nodular goiter. I don't know whether it has any bearing on the general problem or not. The fact that relatives of these patients had nodular goiter is suggestive.

I should like to give you our concept of nodular goiter. In our clinic we think of it as a lifelong disease, beginning or becoming first apparent at adolescence as adolescent goiter. This progresses into middle life when nodular goiter is a common finding. If one follows these patients long enough into later life, the fifth, sixth, seventh decades, he then finds that many of them, perhaps up to 20-30 per cent, have developed toxic nodular goiter. We think therefore that toxic goiter is the end stage of a lifelong process which perhaps, even probably, is constitutionally determined.

This concept has certain implications for therapy. It implies that one does not see simple nodular goiter in childhood. If one does, he must think of other conditions such as Hashimoto's disease or perhaps neoplasm of the thyroid. The concept implies also if one is going to do anything about nodular goiter he needs to do it at its earliest manifestations. Therapy we might discuss later, if indeed there is any therapy. The implication in old age is that one is dealing with a disease which is of life-long duration. One needs to be particularly wary of the possibility in these older patients that the disease has subtly become a *toxic* nodular goiter, with its major impact on the cardiovascular system.

MODERATOR WERNER: Thank you, Dr. Stanbury.

I think you all appreciate what a body of work has been so concisely summarized by Dr. Stanbury.

Dr. Talbot has chosen a rather interesting title for his presentation, *What Price Surgical Versus Medical Treatment of Thyrotoxicosis in Children?*

DR. NATHAN B. TALBOT: There is a great deal of evidence to suggest that you can treat thyrotoxicosis as it occurs in children, as you can in adults, with a high degree of confidence that it can be brought under control by either of the two methods mentioned, namely, by surgery or the use of one of the anti-thyroid agents such as propyl thiouracil. Given these possibilities there is still some question as to which is the best way to handle children with this disease. If you start with the premise that you can carry them equally well by both agents, you might say there is no choice. In a moment or two I should like to present some thoughts on this subject and then leave to you the question as to which is the least expensive from the point of view of the patient.

(Slide) Here, as a starter, is a chart. This chart on the left sets forth in approximate terms the expected course of children treated by these two means. This information is based on a series of 20-odd patients whom we have followed surgically in addition to another group of 20-odd patients followed by Van Wyck and associates by procedures similar to those we use medically and which we believe are sound. If a patient is to be treated surgically, he spends the first two to three months taking propyl thiouracil to render him euthyroid. He then undergoes a subtotal thyroidectomy, following which it has been our custom to place him on USP thyroid for a period of a year to make sure he is maintained in a euthyroid state, since so many of them go through a transient period of hypothyroidism following subtotal thyroidectomy. By the end of the first year, therapy is discontinued for a trial period to see if the patient is still in need of thyroid. As you can see, about half are found to be euthyroid and in no need of further therapy. The other half is found to be hypothyroid and to have a continuing need for thyroid hormone substitution therapy. This need is fulfilled by the administration of 100 mg. of USP thyroid per square meter of body surface per day.

The medical treatment of patients starts out the same way. How-

ever, in this group the propyl thiouracil therapy is continued for a period of about two years. At the end of that time, about 50 per cent of the patients are euthyroid and the other 50 per cent retain their disease in active form. In the case of this group one either needs to continue the propyl thiouracil or at this point revert to surgery.

(Slide) If this is totalled now in terms of months of detailed supervision you see that the surgical patient has a very brief period. This consists of the first two months of therapy, a week of surgery, and then a small amount of medical follow-up. By contrast, the medical patient must be followed in quite considerable detail both to maintain him in a satisfactory euthyroid state and to make sure that he is not suffering from the toxic effects of the drug. As you know, propyl thiouracil may induce leukopenia at any time in the course of its administration, even a year or more after treatment has been initiated. The monetary cost of these procedures seems to be about the same.

The last slide shows that surgically treated patients, if found in need of thyroid postoperatively, can take their thyroid dose once daily at any convenient time.

By contrast, the medically treated: If one gives propyl thiouracil every eight hours by the clock, one is asking the patient to remember to take a pill every eight hours (with only a little leeway) for a total of 2200 times over the course of two years.

Under the surgical regimen the patient who needs thyroid can take it, if he has to take it at all, any time of the day and can skip one now and then without feeling the difference. So I leave you now to consider which would you rather be subjected to, this regimen or the other?

MODERATOR WERNER: Those were the introductory comments. I am now going to ask Dr. Elliott whether a 50 per cent incidence of hypothyroidism is the usual surgical experience at Babies Hospital.

DR. ELLIOTT: I cannot answer that. In recent years we have not seen very many cases of hypothyroidism because it is my impression—I see that Dr. Sloan is here tonight, possibly he can confirm it—that a good many of our children are being treated with antithyroid drugs.

MODERATOR WERNER: It seems to me that a 50 per cent rate is somewhat high as a therapeutic goal for the future. I wonder if one took the trouble to tide these patients over until age 16 or 17, when the gland had become larger and the events of puberty would have passed,

whether one might then get better surgical results. Dr. Talbot, what would you think about this?

DR. TALBOT: We have had no recurrence of thyrotoxicosis in this group. We had many occurrences prior to 1942 when Dr. Cope decided that it would be advisable to eliminate recurrences by doing a very generous subtotal thyroidectomy. Neither have we had any deaths, recurrent laryngeal nerve paralyses, or hypoparathyroidism lasting more than 48 hours postoperatively.

MODERATOR WERNER: I should like to ask Dr. Stanbury, because he sees adult patients, whether the control of hypothyroidism in adults is quite as easy to establish as it is in the younger patient.

DR. STANBURY: The way you phrase your question Dr. Werner, suggests that I should say no, but I think the answer is yes. It is very easy to control adult patients with thyroid at the proper level without any difficulty. I don't know how many hundred patients we have who take thyroid regularly. We rarely have any trouble.

The thing that bothers me about this business is must we take an "either-or" point of view? Is there any other way that a patient can be treated at the pre-adolescent level for thyrotoxicosis besides by propyl thiouracil or by surgery? Is there some alternative method that might be better than either?

MODERATOR WERNER: That is a good point, except that since we don't know the cause of the disorder, we have no treatment directed at the cause, and so no alternative to those you mention. Do you have one?

DR. STANBURY: Yes. A great many patients can be carried on potassium iodide for a long time. At least there are some who can be carried that way. May I pass that question to Dr. Talbot?

DR. TALBOT: We have carried a few mildly thyrotoxic patients on potassium iodide alone, but it was not satisfactory because it was not capable of controlling the disease under conditions of stress. This necessitated curtailment of school and social activities from time to time to such an extent that the children missed a considerable portion of normal childhood pleasures and were obliged to be health-conscious almost constantly.

MODERATOR WERNER: One other point about iodides: If a patient is on iodides and gets a streptococcal sore throat, he is often a candidate for a storm. Then if you try to treat the storm you have virtually no agent which will block the gland because the gland is full of iodine

which has been incorporated into thyroglobulin so that the antithyroid drugs are not rapidly effective. The iodides are useless, obviously, and therapeutically one is left high and dry.

Another point: It is my impression, right or wrong, that the progress of ophthalmopathy with chronic iodide therapy and incompletely controlled toxicity has been greater than in those who received some more acute and definitive form of treatment, barring the occasional very rapid advances after operation and I^{131}.

DR. STANBURY: Is it cricket to bring up radioiodide or are you going to pass it by?

MODERATOR WERNER: This brings up something that we were going to discuss in not quite so impromptu a manner. I should like to ask Dr. Stanbury whether in treating patients with I^{131} or any form of radioiodine, he believes one should keep an age limit of 40, or 45, or older, or whether this precaution should be relaxed and patients at a younger age be treated by this means.

DR. STANBURY: This whole question is a most difficult one. I am sure nobody has the answer to it at this time. There are wisps of evidence here and there, evidence from an excessive number of malformed children among radiologists' families, for example, evidence of roentgen pelvimetry being associated with increased incidence of leukemia and other cancers in children, evidence of thyroid tumors following radiation of the thymus and so on. There is no evidence yet that radioactive iodine has caused malignant disease in patients in the years subsequent to therapy. I think the answer to this problem at the moment has to be almost an emotional one. I don't see any rational way of deciding whether there should be an age limit. There are those who fix age limits—we do in our clinic—an age of 40. There are others elsewhere, equally qualified, who find no justification or necessity for an age limit. I don't know what the answer is.

MODERATOR WERNER: *Dr. Talbot, what would you think of giving radioiodine to children?*

DR. TALBOT: There are several series of reports on carcinoma of the thyroid in pediatric patients who have been exposed to radiation of the head and neck during early life. One series was reported by Duffy. In this series, ten out of 28 young people with thyroid carcinoma had received radiation to the thymus between the fourth and sixteenth months of life. In another series reported by Clark, of 15 patients with

thyroid carcinoma, all had received radiation of the head and neck region when young. Winship had another series of 27 patients with similar exposure. These figures do not necessarily mean that radiation of the thyroid will predispose to malignancy of that gland. On the other hand, if this is a significant possibility, then, I for one, would prefer to avoid use of radioactive iodine therapy in children except when there is some very strong reason for choosing it in preference to chemotherapy or surgery.

MODERATOR WERNER: There is one other factor that has also been brought out by the National Research Council group who met to discuss the dangers of radiation effect,—that is potential genetic damage from increasing radiation exposure. Although Dr. Marinelli in his early studies and Dr. Quimby and others have shown that with therapeutic doses of I^{131}, radiation effect on the gonad is extremely slight in a young person, there is an increased likelihood of genetic injuries expressed as mutants which might possibly appear in the first and later generations as Drs. Mueller and Glass have stated.

Dr. Elliott, do you have any views on this subject?

DR. ELLIOTT: No. I should like to ask Dr. Talbot a question regarding the differences in Dr. Cope's results which you mentioned, in the earlier group and in the later group. I assume that this is probably due to their preparation with the antithyroid drugs in the later group rather than on iodine, or is it? Do you know the reason for this?

DR. TALBOT: I think the improved preparation had something to do with it, but I think the intent of the surgery has also had something to do with it. Instead of trying to take out a quantity of thyroid tissue which would leave the patient euthyroid, since '42 the intent has been to take out enough of the gland so that there would be essentially no likelihood of recurrence. We have been willing to take a chance on the development of hypothyroidism because we consider this an easy disease to treat and one to be preferred over thyrotoxicosis.

DR. ELLIOTT: Another question I would like to ask is this: It is all well and good for the specially trained thyroid surgeon to be chosen for this type of therapy, but do you think that, over the country at large, it would be advisable in general for children to be treated by surgery? That is probably not a fair question.

DR. TALBOT: It is a good question though.

DR. STANBURY: It should be remembered that Dr. Cope has done

many parathyroidectomies and knows how to find them.

DR. TALBOT: Perhaps I did not word it just right. As I said, Dr. Cope has developed the principles upon which thyroidectomies are performed at Massachusetts General Hospital. However, the operations often are carried out by members of the surgical resident staff. This suggests that the good results reported above should be attributed more to good training in thyroid surgery rather than to the exceptional skill of one or two individuals.

MODERATOR WERNER: One should also bear in mind the results reported from the Los Angeles County Hospital and the rate of complications and mortality which followed subtotal thyroidectomy for hyperthyroidism when performed by men who were not quite as well trained or who did not train their residents quite as well as in some more specialized services. The authors of this paper did not write it in order to advertise their bad results, but rather, I think to emphasize the point that Dr. Elliott implied, that not all surgeons operate with equal efficiency.

DR. TALBOT: I would subscribe to that. If a suitably trained surgeon is not available, I believe it would be preferable to treat the patient by medical means.

DR. ELLIOTT: I would certainly not wish to let my branch of the profession down, Dr. Talbot, but I think that this is our attitude at Presbyterian Hospital. We surgeons used to see the ones that were the so-called "medical failures". But I presume that most of these children are now getting well, for we have not seen very many of them in recent years. I was under the impression, rightly or wrongly, that a somewhat greater percentage attained permanent remission with the antithyroid drugs. I gather that I was wrong.

MODERATOR WERNER: I don't think so. I think Dr. Astwood would challenge the statement that only half of the children go into remission. In his series he would tend to infer about 70 or 80 per cent are apt to go into remission.

DR. TALBOT: I don't want to engage in controversy but I believe that, with respect to children, data available at this time indicate that chemotherapy will not yield more than 60 per cent permanent remissions after two solid years of therapy.

MODERATOR WERNER: To summarize this discussion, it would appear that Dr. Talbot believes that from the psychological standpoint the

use of a really advanced subtotal, practically total, thyroidectomy in the hands of a competent surgeon is the most efficient method for treating juvenile hyperthyroidism; that the minority here is inclined to feel that a high incidence of hypothroidism is not desirable, and has also pointed out that the quality of surgery varies throughout the country so that there are areas where the risks of surgery are perhaps too great to recommend such an approach. Is that a fair statement?

DR. TALBOT: The only thing that I quarrel about with you is that I did not draw any conclusions. I left it to you.

MODERATOR WERNER: I said "it would appear".

I think we had better turn to another subject and I will ask Dr. Elliott whether he believes that all patients with non-toxic nodular goiter deserve surgery and, if not, how should one select those who do?

DR. ELLIOTT: This is the $64,000 question. No, I certainly don't believe that all patients with non-toxic goiter should be operated on. I think that this is largely a matter to be determined by the judgment and experience of the individual who sees the patient. My own feeling is that the smaller, soft, glands, without any particularly dominant nodule, are probably best left alone. In my opinion, those that are causing trouble, by producing either toxicity or obstruction, or where the surgeon or the internist is concerned about cancer, should be operated upon. In the older age group in the seventies and eighties, I think we are justified in watching some of the nodular goiters, even those of fairly large size. I am afraid I have hedged on that one.

MODERATOR WERNER: *I was going to ask, Dr. Stanbury, is there a place for I^{131} in the treatment of nodular goiter?*

DR. STANBURY: In non-toxic nodular goiter, I think not, except perhaps under extraordinary and rare circumstances. It does have a place in toxic nodular goiter.

MODERATOR WERNER: *Dr. Talbot, what is the problem in children? Would you recommend surgery for all children with non-toxic nodules in their thyroid?*

DR. TALBOT: In practice we try to determine whether the administration of dosages of thyroid shrinking hormones will cause the gland to shrink away. If we are not successful, we believe we should know what is there.

I should like to ask Dr. Elliott his opinion of needle biopsy.

DR. ELLIOTT: I think I am on fairly safe grounds. As far as the

surgical profession at large is concerned, the conviction is widespread that neither needle nor incisional biopsy into a nodule is advisable if malignancy is suspected. One only tends to spread the disease by so doing. It is often hard enough for the pathologist to give us a diagnosis with the whole gland. If he has only a small fragment of tissue out of a needle to work with it is that much more difficult.

MODERATOR WERNER: Dr. Talbot raised the question of thyroid in the treatment of nodular goiter and I believe the work of Dr. Astwood and Dr. Greer has brought out the fact that non-toxic goiter can usually or often be successfully treated by medical means. In a non-toxic goiter of the nature that Dr. Stanbury just described, where there is an enzymatic defect or an incomplete product being turned out by the gland as a consequence, obviously, the replacement of the missing thyroid secretion by exogenous thyroid hormone will serve to suppress the pituitary and cause the goiter to shrink. As far back as the eighteen nineties, a physician made the observation in a nunnery in Germany where goiter was practically endemic that the goiters could be readily made to disappear by giving sheep thyroid gland. Drs. Greer and Astwood carried this one step further and began to treat nodular goiter as well as diffuse goiter with exogenous thyroid substance and obtained a definite incidence of shrinkage of the nodules, but only about a 10 per cent disappearance of nodular goiter.

The questions one has to ask oneself are: What is happening in these cases of nodular non-toxic goiter; and what about the patients whose non-toxic nodular goiter may be complicated by possible carcinoma or by a benign adenoma with which, as Dr. Sloan has pointed out, there is a high incidence of associated cancer? Dr. Frantz has also pointed this out. I should like to ask Dr. Elliott what he thinks of this therapeutic method advocated also by Dr. Crile, of treating with thyroid, even with the risk of cancer in the gland.

DR. ELLIOTT: At the present time, I personally would not feel too happy about carrying a patient on thyroid for any great length of time if I suspected cancer. We are at the moment engaged in a program at The Presbyterian Hospital Thyroid Clinic of feeding thyroid to most of the non-toxic nodular goiters and even to those with solitary nodules, for a period of about two months. If the nodule disappears, well and good; but if it persists at all and even though it shrinks appreciably we plan to operate and see just exactly what the pathology is.

That is the present state of both our thinking and our program.

MODERATOR WERNER: *Dr. Stanbury, what do you think of this movement to give thyroid?*

DR. STANBURY: One's opinion is always colored by what he has seen recently. This past week we saw a nurse in our clinic with papillary cancer in the neck who was treated for a year with thyroid for the nodule. I don't think this has changed the thinking of the clinic. We don't see the shrinking with thyroid of nodules which have been there for any appreciable period of time. We have tried enough of them. We should have seen some of them disappear if they would. It is a very rare instance where we can honestly say that there is a detectable shrinkage with full dose of thyroid. We are unwilling to treat single nodules with thyroid. We take them out.

MODERATOR WERNER: *Dr. Talbot, do you have any views on that subject?*

DR. TALBOT: One of the types of nodular goiter we see in pediatric practice is more fairly described as a lobular type of nodular goiter that turns out, in a good many instances, to be Hashimoto's thyroid disease. If one gives those patients heavy doses of thyroid the gland does tend to shrink and more or less disappear. This is one group in which we don't hesitate to delay surgery to this extent, and give thyroid in suppressive doses. It is effective quite rapidly if the dose is high enough. In children it takes more thyroid to cause shrinkage of the gland than it does to render that child euthyroid. If the thyroid were removed entirely, we use about 100 mg. of thyroid per square meter per day as a common denominator. That is an adequate therapeutic dose. With the hypothyroid dose to suppress the goiter it may require 120 to 150, rarely to even 180 mg., per square meter per day. A child of nine years, weighing 70 pounds, 30 kilograms, is one square meter. Just to orient you, an adult is between one and one-half to two square meters, which gives you some notion. But when the nodule is very hard and causes considerable suspicion, I think we also feel it is worth being looked at.

We did have an interesting exception to that recently when a child presented a stony hard goiter, which turned out to be due to cobaltous chloride. So one should be sure one is not dealing with a goitrogen, which, when removed, cures the malady.

MODERATOR WERNER: I was going to make a similar comment. It

seems to me that the nodules I have seen disappear were probably in patients who really had thyroiditis, chronic thyroiditis, rather than true nodular goiter. But I think operation proves that 50 per cent shrinkage occurs at least in a number of bona fide nodules.

However, there is one physiologic point. If one gives a substance like triiodothyronine, and measures iodine uptake before and after the drug, in the usual patient with non-toxic nodular goiter, one obtains a suppression of uptake. There is about one patient in four however, in whom I^{131} is not suppressed. One has the impression that these are the patients with the active nodules which will follow the life history outlined by Dr. Stanbury. Giving thyroid to these people probably would be a waste of time since they presumably are independent of pituitary control.

As long as Dr. Talbot has brought up the subject of thyroiditis, here is a question as to what his explanation is for the discrepancy between the butyl extractable iodine and the serum precipitable or protein bound iodine in that disorder. Dr. Talbot demonstrated several years ago that if one did just an ordinary protein bound iodine, one found normal levels in children with Hashimoto struma, whereas if one did a butyl extractable iodine determination, one found these patients were in the hypothyroid range or at least appreciably low. Dr. Talbot, what is your latest view about this discrepancy?

DR. TALBOT: The thyroid gland is not working right, Dr. Werner. I would like to turn that question back to you. I think there is an explanation.

MODERATOR WERNER: *Dr. Stanbury, would you like to answer that?*

DR. STANBURY: Are you talking about material at the origin in electrophoretograms?

MODERATOR WERNER: *No. Paper chromatograms.*

Owen and McConahey at the Mayo Clinic have shown that the large fraction of the proteins on paper chromatography remained at the origin with butanol as the solvent. This could be interpreted as thyroglobulin released by the thyroid. Thyroglobulin would be determined by the protein bound iodine method but would not be found in the butyl extractable procedure.

In that connection also, Skillern at the Cleveland Clinic found that one can, by using thyrotropic hormone, make a diagnosis of chronic thyroiditis with considerable accuracy. He gives a single injection of

thyrotropic hormone and then measures I^{131} uptake and serum precipitable iodine. The patients with chronic thyroiditis do not show an increase in serum precipitable iodine or I^{131} uptake as opposed to patients with non-toxic goiter who do show an appreciable increase.

Dr. Stanbury, do you use the thyrotropic hormone as a test agent with any frequency at the Massachusetts General Hospital?

DR. STANBURY: Once in six months or once in a year.

MODERATOR WERNER: *What do you think of the work of Jefferies and his group, in which they tend to find low thyroid reserve by giving thyrotropin?*

DR. STANBURY: It is a very interesting finding. When I heard Dr. Jefferies present this material at the meetings last spring I was very curious to know the values for the serum protein bound I^{131}. They had not measured this. It would have been of great interest had they known whether the glands were under maximal stimulus, because in many cases they might have found the glands were not resting at all but were working at maximal capacity. They could have shown that with I^{131}.

MODERATOR WERNER: That is right. What they were attempting to show in patients with thyroiditis or advanced disease of the thyroid, by giving thyrotropin, was such a limited response of uptake or of iodine release, that the gland had to be highly diseased throughout.

Here is one question pertaining to thyroid cancer in the older patient, and in the younger patient. We are inclined nowadays to dismiss thyroid cancer as not being a very serious disease. We hear that thyroid nodules of the Group I variety will have a life history of 20 years, or more in some instances. I wonder, Dr. Elliott, whether that is true of the patient over 50, or whether one sees a different type of life history.

DR. ELLIOTT: That is not too easy a question to answer. By and large, in the older group the thyroid cancers are apt to be more malignant. As I intimated earlier, we have no Grade III's that I know of under age 49. It is quite true that some of the old people can carry metastases for a very long period of time and die from some other cause, but in general I would feel that the disease is more malignant in the older groups.

As far as the earlier years of life are concerned our attitude has been —and we have not seen too much of the really widespread type of cancer in children—that the lesion should be removed surgically but the

child should not be mutilated.

You may say, "What do you mean by 'the child should not be mutilated'?" I mean by that, that where possible, the sternomastoid muscles should be spared, and when possible, at least one of the two jugular veins. In summary, as far as children are concerned, we believe that they should be approached surgically in much the same fashion as the adult, but with somewhat more emphasis directed toward the cosmetic result.

MODERATOR WERNER: *Dr. Talbot, is it your impression that thyroid cancer in the young, say under the age of 11 or 12, is a more virulent disease than after that age?*

DR. TALBOT: We have seen it both ways. When it is in a malignant form, it is a very disconcerting disease in the young.

MODERATOR WERNER: *Dr. Stanbury, what is your impression about this? Do you think there is an age discrepancy, that cancer is more benign in middle age groups and more extreme in the older and younger ages?*

DR. STANBURY: Dr. McDermott, of our group, has been analyzing our results for several years now and he has drawn life expectancy curves on thyroid carcinoma. The curve would suggest it is a far more serious matter in the older age group than in the young. This is papillary carcinoma. A few years ago we lost a 16 year old girl with papillary carcinoma which surely can be, as you indicated, a lethal disease at that age. In the aggregate, it does seem to be a more serious problem in the older age group.

MODERATOR WERNER: I think Dr. Sloan and Dr. Frantz have brought out that if one views this disease from the standpoint of its duration, that one finds a marked correspondence between duration of disease and the future projected life history. The patient may have had cancer for 20 years when first seen and so may have a short life expectancy whereas the patient seen early in the disease will tend to have a long expectancy. Yet both may experience the same duration of disease. On the other hand, it does appear to be a clinical fact that by the time people reach the older age groups, they do seem to have a more rapid downhill course, even allowing for this fact. Again, as Dr. Talbot mentioned, some of the younger patients may have an extremely abrupt course.

In the field of thyroid cancer, would you tend to give the same

prognosis to adenoma malignum or adenocarcinoma of the Group I variety as you would to papillary carcinoma, Dr. Elliott?

DR. ELLIOTT: I can only quote you some figures from a series at Presbyterian Hospital. Of the alveolar carcinomas about 25 per cent had died; of the papillary carcinomas the figure was around 13 per cent, so that at least in this series there did seem to be a difference. But, on the other hand, I think it should be pointed out that in recent years at Presbyterian Hospital our pathologists have not often been making a single diagnosis. The tumors seem usually to be mixed papillary carcinoma and adenoma malignum, not only in the gland but often in the metastases. So that it is becoming increasingly difficult to separate these two groups as we go along.

MODERATOR WERNER: *In view of that, Dr. Stanbury, how does one proceed after a radical neck dissection has been done for papillary or possible mixed carcinoma?*

DR. STANBURY: If you have satisfied yourself that no metastases are determinable, I believe all you can do is wait and see. Beyond that I would not know what to do. I suppose, if you wished, you could try a survey of the spine and the rest of the bones after radioactive iodine administration. This perhaps would be worth doing. The main thing after the radical neck operation is to wait and see if any metastases appear. If so we take them out. We have done a good deal of that. We have taken off parts of the calvarium and other parts with some success.

MODERATOR WERNER: *Would you advise total lobectomy even if the patients had one lobe previously removed, when there is papillary cancer? Would you try to remove the other lobe with a view towards making these adenocarcinomatous areas acceptable for I^{131} therapy?*

DR. STANBURY: Would you remove the other lobe? You removed one side, not the other. I think you can take your choice. If the thing had not extended very far, you could try burning out the remaining lobe with radioiodide. Pochin does that. You can take it out. I don't know that it makes a whole lot of difference.

MODERATOR WERNER: *I shall ask Dr. Elliott what he thinks.*

DR. ELLIOTT: We believe that if a positive diagnosis of cancer is reported by the pathologist during operation that we are on much safer ground if the entire thyroid gland is removed. Our reason for this is that we have encountered a number of instances of papillary cancer in which there have been multicentric foci of tumor in both lobes. So

we believe that there are two reasons for performing total ablation. One is the possibility just mentioned of multicentric foci being left behind in the opposite lobe, and the other the fact that total thyroidectomy is better preparation for future isotope therapy.

DR. STANBURY: If the neck had already been closed by the surgeon and you got your report—that is the way you phrased the question?

MODERATOR WERNER: With one lobe left behind.

DR. ELLIOTT: I see. I did not understand that. Under those circumstances if we can get the original slides and get some idea of the nature of the tumor, and if we feel fairly certain that there are probably no metastases on the side that has been removed, we may observe for a while, but my own belief is that these patients are better off if they have the other side removed. I think it is safer.

MODERATOR WERNER: *Dr. Talbot, would you have anything to say on this?*

DR. TALBOT: If one lobe is left behind, the classic thing to do would be, with present knowledge, to complete the lobectomy, do a second lobectomy and give I^{131} and determine if there is significant retention within the body.

MODERATOR WERNER: We should bear in mind the demonstration of Dr. Crile and Dr. Astwood who by giving thyroid have actually seen regression of pulmonary metastases from papillary carcinoma. If this is true, then one might determine if suppression of the pituitary will make these tumors, which may possibly still be hormonally dependent, recede. Dr. Furth has shown that in experimental tumors many of them are hormonally dependent at the earliest stage of their development. These are pituitary tumors. Then after several transplants these tumors become hormonally independent. For instance, with the thyrotropic tumors, as long as they are hormonally dependent, removal of any stimulus or administration of thyroid will cause regression of the tumor but the minute they become hormonally independent then all these measures are futile. Now it may well be that among the papillary tumors, a number are hormonally dependent. If such is the case, either an absolute hypophysectomy by surgery, or functional hypophysectomy by giving thyroid, might conceivably result in very significant disappearance of these metastases. That is something which we must watch with much interest.

MODERATOR WERNER: *Dr. Talbot, I have one more question for you*

which has not yet been answered. How do you treat juvenile non-toxic goiters, so-called adolescent goiters? Do you leave them alone or treat them?

DR. TALBOT: We have tended to give pituitary-suppressing doses of thyroid and the goiter be made to disappear. However, after having listened to these comments about the capacity of the thyroid to suppress not only normal tissue but also malignant tissue I am wondering whether we may not some time, some day, be riding for a fall on this philosophy. On the other hand, these adolescent buds are usually rather smooth and they need not concern you too much with regard to nodularity. We treat some, and in others proceed in a desultory manner. I rather think that the majority of mild, borderline adolescent goiters that we see could probably just as well be left alone because they seem to take care of themselves. The more sizable ones probably would be much better off if kept on the suppressive thyroid for a long period of time and might never arrive at the late stage of the cycle where they come to the surgeon. What do you think about that, Dr. Elliott?

DR. ELLIOTT: That sounds reasonable to me. I would say that our general policy with regard to non-toxic diffuse goiter has been to leave the gland alone. Of recent years particularly, use of thyroid replacement therapy in these cases seems to have met with considerable success. We do not as a rule remove these glands unless they are of unusual size or are causing obstructive symptoms.

MODERATOR WERNER: *Dr. Stanbury have you any views about the production of adolescent goiter?*

DR. STANBURY: I think it is a constitutional disease of some sort, but that is just begging the question. We have to define what "constitutional" means sooner or later. I don't really have any answer to the question. I think here in this part of the world it has nothing to do with iodine deficiency.

MODERATOR WERNER: *Do you think other readjustments at the time of puberty have anything to do with goitrogenesis?*

DR. STANBURY: I strongly suspect that they do.

MODERATOR WERNER: There is one other important question with regard to nodular goiter. Recently Dr. Perlmutter and others have proposed that if by scanning the thyroid after giving I^{131} with an automatic scanning apparatus, one finds areas of low activity, one should be extremely suspicious that such an area is malignant. The procedure

sounds fairly straightforward. One lets the apparatus go back and forth over the neck and all one has to do is pick out an area that is not active. If such an area is found then one operates on the patient. This detection of cancer assumes great importance because recent figures from the Ochsner Clinic and the figures from Brown and his co-workers, tend to imply that as much as 25 per cent, 20 per cent at least, of non-toxic multinodular goiters have histologic cancer associated with them.

I want to ask Dr. Stanbury what he thinks of the simplicity or reliability of this scanning procedure and then I want to ask Dr. Elliott and Dr. Talbot what they think of Dr. Frantz' expression "pathologist's versus clinician's cancer" in interpreting the meaning of this recent increase in incidence of thyroid cancer histologically. Dr. Stanbury!

DR. STANBURY: In our clinic we don't have an automatic scanner such as Perlmutter is using. We have a hand operated device which has been used for some time in developing the concept of cold and hot nodule versus cancer. I think Brown Dobyns had this idea first. It has statistical validity. There are certain exceptions. The hot nodule is rarely cancerous, but occasionally it is. The cold nodule does have a high incidence of cancer but many of them are benign. The figure—what did you say?

MODERATOR WERNER: *Twenty per cent from Dr. Ochsner. Dr. Brown's came out between 15 and 20 per cent.*

DR. STANBURY: Purely clinical multinodular goiter would be one per cent or less.

MODERATOR WERNER: *Do you use this scanning apparatus?*

DR. TALBOT: No.

DR. ELLIOTT: No.

MODERATOR WERNER: I should like to point out that a nodule is often surrounded by normal thyroid tissue. Therefore you may have a nodule that is as cold as it could be and yet back of it have a large thick mass of normal thyroid tissue which has taken up a good deal of radioiodine and emits gamma rays which easily penetrate a small nodule to reach the counting crystal. Thus one may be led astray by a false sense of security concerning the nodule. On the other hand, there may be circumstances where the converse holds. So I don't think this procedure is completely reliable. Also, one finds that one has a perfectly simple non-toxic nodule and yet behind the nodule will be a microscopic tumor which one could not possibly identify by clinical methods.

This brings up the next question:—What is the relative incidence of thyroid cancer as diagnosed by the pathologists, compared with that diagnosed clinically? Dr. Stanbury has already implied from their figures that clinical cancer is very much less. What do you think of this question?

DR. ELLIOTT: As I mentioned in my opening remarks, this is one of the problems that is bothering the surgeon profoundly today, because there seems little doubt but that pathologists all over the country are finding more and more of these microscopic or clinically undetectable small cancers. This is very beautifully brought out in a series of a thousand consecutive and unselected autopsies from the Mayo Clinic which was reported by Mortensen, Bennett and Woolner in the Forum of the American College of Surgeons several years ago. These observers found, in going over the thyroids in this series, that there were 46 malignancies in the one thousand thyroid glands of these patients. These glands were completely and serially sectioned in very thin saggital slices, after they had been first examined in the usual manner by the regular pathologists. The glands were then turned over to a special team which went over the saggital slices. Of these 46 malignancies in a thousand thyroids, 28 were primary in the gland proper and 18 were metastatic malignancies from elsewhere in the body. Only one of these thousand patients died of thyroid carcinoma and that carcinoma was the only one in the series recognized clinically. Only two of the primary carcinomas in these patients were picked up by the regular pathologists. In other words, 27 of 28 primary thyroid cancers were unrecognized by the clinician and 26 of 28 by the regular pathology team. It was only when a special team went to work and serially sectioned these glands that all these other little tumors were found and I am wondering whether this is not what is happening around the country. Pathology laboratories seem to be intensifying their search for these smaller tumors and frankly I don't know what their significance is. I doubt that anyone knows their true significance at this point.

DR. STANBURY: Could it be over-reading of sections?

DR. ELLIOTT: It could indeed. It does nonetheless put the surgeon in a bit of a quandary, for this problem seems to be coming up with increasing frequency. One rarely feels justified in advising immediate reoperation on a patient who has had a partial thyroidectomy for a non-toxic nodular goiter in which one of these small, incidental tumors

is discovered postoperatively. Our policy has usually been to follow the patient closely and to await developments.

MODERATOR WERNER: *Dr. Talbot, if you were given a diagnosis of thyroid cancer in a child, would you accept that at face value?*

DR. TALBOT: Yes, I have no choice.

MODERATOR WERNER: One would conclude that the situation was different in a child than in an adult with multinodular goiter and I think that the seriousness of thyroid cancer is greater in a child than in an adult.

I believe this concludes our comments. I should like to thank all the panelists for this excellent discussion of a very interesting subject.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting on March 28, 1957, at The New York Academy of Medicine

The Significance of Hydropic Degeneration in the Diabetic Pancreas

SYDNEY S. LAZARUS AND BRUNO W. VOLK

Isaac Albert Research Institute of the Jewish Chronic Disease Hospital and the Department of Pathology, Albert Einstein College of Medicine, New York

Vacuolization, or so-called "hydropic degeneration," of the beta cells of the islets and of duct epithelium is one of the few specific morphologic alterations of the pancreas which may be found in both human diabetes mellitus and in experimental diabetes in animals. Because it was not possible with the techniques then available to demonstrate fat or glycogen or other material in swollen vacuolated cells this lesion was considered originally to be a degenerative one, due to imbibition of fluid. From studies on partially pancreatectomized dogs Allen advanced the hypothesis that during the development of diabetes the beta cells are stimulated to increase their insulin output until they become functionally exhausted. Morphologically, this was thought to be evidenced by the "hydropic degeneration" of the beta cells. This hypothesis did not, however, explain the concomitant vacuolization of pancreatic ductular epithelium, since the latter cells have no known endocrine function. In an attempt to find a common pathogenetic denominator it was suggested that the ductal lesion could be considered as being due to "exhaustion of a proliferative function". Most subsequent workers emphasized the beta cell hydropic degeneration as a characteristic lesion of the pancreas in experimental diabetes resulting from functional overstrain. In many instances the duct epithelial vacuolization was not reported or remained as a more or less unexplained concomitant.

Recently it has been shown that glycogen is contained in the vacuolated pancreatic beta cells and ductular epithelium in experimental and human diabetes mellitus. The characteristic appearance of the hydropic cells is attributable to artefactual removal of the intracytoplasmic accumulations of glycogen rather than of excessive quantities of water. It was suggested that this glycogen accumulation might represent merely one component of the widespread pathologic glycogen deposits found in diabetes or alternatively that it might be indicative of proliferative activity of duct epithelium with deranged islet regeneration. More recently it has been demonstrated that in cortisone-induced diabetes in rabbits ductular glycogen infiltration actually precedes these changes in the beta cells. This observation seemed almost to exclude the "functional exhaustion" hypothesis of hydropic change, unless the lesions of the beta cells and those of the duct epithelium could be thought of as being distinctly separate and of different etiologies. This latter idea is negated, however, by known facts. This finding was considered, therefore, to indicate that the pathogenetic mechanism for pancreatic glycogen deposition in diabetes was similar to that for other organs and was related to increased glucose transfer across

cell membranes in the presence of hyperglycemia.

It was considered of importance to determine whether as a general phenomenon for various types of experimental diabetes ductular glycogen deposition precedes that in beta cells. For this purpose experiments were carried out in rabbits and in dogs. The rabbits were divided into two groups. One group received 5 to 10 mg. per kilo of hydrocortisone acetate daily intramuscularly for one to 28 days. The other group was given 3 mg. per kilo of hydrocortisone acetate daily in conjunction with 1 mg. per kilo of growth hormone subcutaneously for periods of up to 14 days. The dogs were divided into four groups. The first group received 3 mg. per kilo of purified pituitary growth hormone subcutaneously for periods of up to 14 days. The second group was subjected to 85 per cent partial pancreatectomy only. The third group also underwent 85 per cent partial pancreatectomy; however, after a recovery period of one week each dog received 8 mg. per kilo of cortisone acetate intramuscularly daily for periods of up to four weeks. An additional two dogs were treated similarly except that after three weeks of cortisone they were given 3 mg. per kilo daily of growth hormone for periods of up to 19 days. Control experiments were carried out on normal rabbits and dogs. The animals were sacrificed at various time intervals and the morphology of the pancreas was compared with the degree of diabetes.

In the present study it was found that vacuolization due to glycogen deposits is normally present in the ductular epithelium in the adult canine pancreas, while it is absent in the untreated rabbit. In both the rabbit and dog during the development of diabetes, by whatever method produced, vacuolization of duct epithelium due to glycogen infiltration appears prior to and in the absence of the appearance of glycogen in the beta cells. The glycogen was found in the beta cells of both animal species only at a comparatively late stage.

It may be concluded from these experiments that the prior deposition of glycogen in duct epithelium is a general phenomenon for various types of diabetes. Since obviously no stimulation of ductular secretory function can be postulated, these observations are in strong opposition to the concept that hydropic degeneration is the histologic expression of a degenerative process which results from functional exhaustion. The predominance of glycogen deposition in the ducts over that in beta cells also makes very unlikely the concept that a peculiarity of beta cell metabolism related to insulinogenesis is the pathogenetic mechanism. It would seem more logical to consider this morphologic change as being merely one facet of the ubiquitously increased cellular glycogen deposits that are known to occur in diabetes and similar to those observed in renal tubular epithelium and in muscle, especially of the heart. The explanation for the initial appearance of glycogen in duct epithelium is not known. However, it may be related to an increased glucose concentration in the external pancreatic secretion in the diabetic animal.

This change in viewpoint, that beta cell vacuolization rather than being a degenerative lesion due to exhaustion is merely glycogen infiltration as a consequence of hyperglycemia may have further implications. In other situations glycogen may accumulate within cells without causing their destruction. It, therefore, seems that the present concept that glycogen infiltration in the beta cells is part of the pathogenetic mechanism which leads to their disintegration and to permanent experimental diabetes may have to be revised. However, at present no alternative explanation is available.

DISCUSSION

EUGENE L. OPIE: Is it possible to bring the glycogen deposit into relation with the beta granules?

SYDNEY S. LAZARUS: The original explanation for the development of hydropic change was that in the process of exhaustion of beta cells the first morphologic alteration seen was degranulation, which was considered an early sign of increased function of the beta cells. Supposedly when the beta cells become completely exhausted, they then develop hydropic degeneration. We know

that beta cell degranulation is a sign of stimulation of beta cells to increased insulin output, and it seems rather unfortunate that both these changes take place apparently under the stimulus of hyperglycemia, and that beta cell degranulation occurs rather earlier in the course of events than does the deposition of glycogen within the cell. However, it is my personal feeling that these two phenomena are not pathogenetically related, except insofar as they both reflect to a cer ain extent the presence of hyperglycemia.

BRUNO W. VOLK: I should like to answer Dr. Opie's question further by adding that it has lately been observed that the sulfonylureas produce frequently complete degranulation of the beta cells in the absence of vacuolization and glycogen infiltration. I believe that this may answer his question at least to some degree.

MAX WACHSTEIN: I should like to ask whether there is any relation between the deposition of glycogen in the pancreas and the blood sugar. It has been shown that in rats the deposition of glycogen is dependent upon the height of the blood sugar. The reversion of high to normal blood sugar levels is accompanied by the disappearance of histochemically demonstrable glycogen in diabetic rats.[1] The deposition of glycogen in the kidney obviously follows the overloading of the glomerular filtrate with sugar. It is, however, not clear as yet why in the human diabetic kidney the glycogen is deposited mainly in the terminal portions of the proximal convoluted tubules and in experimental animals in the ascending limbs of Henle's loops, as has been demonstrated by Oliver.[2] Have you any idea why glycogen is so selectively deposited in the ductules and the beta cells of the pancreas in your experimental animals?

SYDNEY S. LAZARUS: Dr. Wachstein's question is really to the point. The fact that glycogen appears earlier in the ductular epithelium might be due to the fact that the concentration of glucose in the external pancreatic secretion is directly related to the concentration in the blood. This may result in increased absorption of glucose by the duct epithelium from the external pancreatic secretion which is converted to glycogen. Then we come to the problem of why after glycogen is present in the ductular epithelium, do we next see it in the beta cells? For this at the moment there is no ready explanation, except for the fact that on rather careful examination of slides it may be seen that when there is only a small amount of glycogen in the cell, this little bit is present at the capillary pole. It therefore probably appears in the beta cells more or less selectively after the duct epithelium because of the high vascularity of the islets. In one of the slides I showed there was glycogen in the acinar epithelium, and in some other of our animals we also found glycogen in other places in the pancreas, so that I do not think this can be considered a selective thing for the beta cells.

As for the blood sugar level at which this phenomenon appears, this question leads to the problem of how we estimate the severity of diabetes. Apparently there are two factors involved. One is the height of the blood sugar, and the other is the length of time this high blood sugar is maintained. With a lower elevation of blood sugar of longer duration we may find glycogen only in the ductular epithelium; with a very high elevation of blood sugar of shorter duration we may find glycogen in both ductular epithelium and beta cells.

SIGMUND L. WILENS: I did some work with Dr. Stumpf[3] a couple of years ago, in which we injected rabbits intramuscularly with cortisone over a long period. We found quite frequently that the acinar tissues were considerably damaged and in some instances there were peripancreatic fat necroses. The islets also were hyperplastic, but as far as we could make out, the acinar change was not related to the islet one. Have you noticed such acinar change, and do you feel that it is associated with the diabetic state in these animals?

SYDNEY S. LAZARUS: While at Queen's University Dr. Bencosme and I worked on the effect of cortisone on the rabbit pancreas. We observed similar phenomena, and were quite puzzled by the pres-

ence of these changes in the exocrine tissue. Eventually we came to the conclusion that they were not related to the diabetes. They may have had to do either with the development of infection in animals treated with cortisone for long periods, or perhaps they might have had to do with changes in the salt and water balance. Animals treated with cortisone over a long time develop within the ductular epithelium inspissated secretion and ductular proliferation occurs, the same as after ligation of the pancreatic duct. However, when you ligate the main pancreatic duct, this occurs generally throughout the entire pancreas. When you give cortisone it is confined to individual lobules. Many people who have administered cortisone have interpreted the proliferation of ductular epithelium as part of a process of new formation of beta cells under the influence of the cortisone. In our work we could not substantiate that interpretation and came to the conclusion that it was related to the development of infection, or else was due to ductular obstruction because of changes in viscosity of the secretory material in the duct lumina.

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Pancreatic Morphology in Diabetic Animals and Man

(Abstract)

W. STANLEY HARTROFT

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Extensive quantitative and qualitative investigations of the morphology of the islets of Langerhans in man and in animals have established many criteria for their normality. Advances in tinctorial techniques have confirmed and extended the earlier investigations. Further advances in the morphology of the pancreatic islets will probably come from application of electron microscopic techniques. Some early results in this field obtained by Dr. Paul Lacy in our laboratory were briefly presented.

Diabetes can be produced in experimental animals by a variety of methods including surgical, hormonal, and toxic. All result in destruction or removal of either beta cells or their granules with an accompanying decrease in amounts of extractable insulin. There is no method of producing experimental diabetes in an animal which leaves a significant amount of insulin in its pancreas at autopsy or significant numbers of granules in its beta cells. This fact is in sharp contradistinction to the universally conceded failure to demonstrate significant pathologic lesions in the islets of probably one fourth of all adult diabetics coming to autopsy. Although insulin and beta cell granules in the pancreases of adult diabetics are significantly less than in non-diabetics, there is considerable overlap between the two groups, and many diabetics, unlike the experimental animals, have pancreases that contain appreciable amounts of both extractable insulin and beta cell granules. Juvenile diabetics differ, however, in that almost without exception little or no insulin or beta cell granules can be found in their islets. Demonstrable lesions in the islets of adult diabetics include various degenerative changes of the beta cells accompanied by degranulation, basement-membrane reduplication, hyalinization and fibrosis. At certain stages at least, the hyalinization is accompanied, if not preceded, by rather striking degrees of fatty degeneration. It is possible that all these various abnormalities represent stages in the progression of a single type of lesion. Recent mensurational evidence substantiates the impressions of earlier observers that in the pancreases of some diabetics islets may regenerate, a reassuring note to those who have not given up searching for the factors that control islet hyperplasia, thus offering hope for discovering a cure of the disease for at least some individuals at some future date.

DISCUSSION

EUGENE L. OPIE: I have had for some time the impression that histologic study of the pancreas with diabetes had gone out of fashion, but what I have heard tonight has changed this opinion. We have had from Dr. Hartroft an illuminating review of important observations that have been made recently by him and his associates, and from Dr. Lazarus and Dr. Volk have learned the cause and nature of the glycogen deposit in the organ. Dr. Hartroft has shown that the electron microscope opens new fields of investigation in pathology. His electron microscopic picture of beta cells with alloxan diabetes makes the sequence of events quite obvious. As he has pointed out, it explains the hypoglycemia, presumably referable to the escape of insulin, that occurs in rabbits following alloxan administration. Destruction of the beta cells is evident, whereas other islet cells escape.

With regard to degenerative changes in

the islets, destructive changes like hyaline degeneration or fibrosis should be regarded as the end-results of severe injury of islet cells which has occurred earlier. Lymphoid infiltration of the islets has been described repeatedly, especially in young persons. It is presumably the result of an injury that has brought about an inflammatory reaction. The electron microscope will perhaps reveal these changes.

I have long been impressed with the importance of hyperplasia of the islands of Langerhans in association with diabetes mellitus. The islet cells in contrast with those of the acini have astonishing ability to regenerate under some conditions. The pancreatic lesion with diabetes, as we see it at autopsy, is the end-result of a balance between destructive changes affecting the islands and regeneration of them. The frequency of normal islands with diabetes as revealed in the statistics of Shields Warren in the first two editions of his book is much greater than that obtained from earlier American and German reports. In the third edition, with LeCompte, normal islands of Langerhans in a considerably greater number of cases are found even more frequently. It may be possible that insulin gives opportunity in some cases for regenerative changes in the islands and actual cure of the disease.

BRUNO W. VOLK: We are all familiar with the work Dr. Hartroft carried out in association with Dr. Wrenshall on the quantitation between the beta cell granules and insulin concentration of the pancreas. Dr. Hartroft mentioned that he and his associates with the aid of the electron microscope were able to follow the breaking up of the beta cell granules. I wonder whether he has been able to follow the insulinogenic function of the beta cells by subjecting these cells to overstrain, thereby studying the development of the beta cell granules under various experimental conditions.

W. STANLEY HARTROFT: The size of beta cell granules appears to vary with certain physiologic and non-physiologic stimuli. Rats were stomach-fed glucose in water and killed at various intervals (30 minutes to 3 hours), starting out with a starved animal. Sections of pancreas were stained with aldehyde fuchsin technique. Degranulation of beta cells did not occur under these physiologic conditions, but the granules were smaller in the animals that had received the glucose. Dr. Lacy is repeating this experiment with the electron microscope, and actually measuring the size of the granules.

SIGMUND L. WILENS: There is a principle in endocrinology that the parenteral administration of a hormone will affect the tissues that ordinarily produce that hormone. What effect, if any, do you think that the prolonged administration of insulin has on the morphology of islet tissue?

W. STANLEY HARTROFT: I have seen in my own experiments with rats which have had large doses of insulin for quite a long period of time, some degranulation of beta cells, although not to a striking degree.

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TUESDAY February 11 1958	COMMON UROLOGICAL PROBLEMS IN GENERAL PRACTICE *Moderator:* VICTOR F. MARSHALL
TUESDAY March 11 1958	MANAGEMENT OF HEMORRHAGIC STATES *Moderator:* LOUIS R. WASSERMAN
TUESDAY April 8 1958	EVALUATION AND MANAGEMENT OF FATIGUE *Moderator:* To be announced

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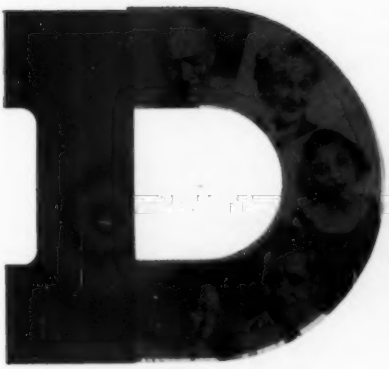

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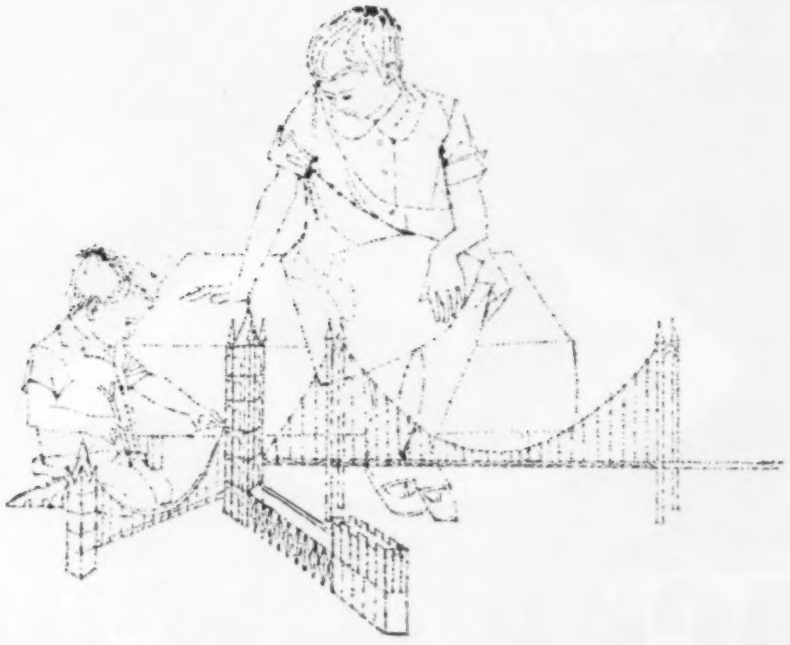

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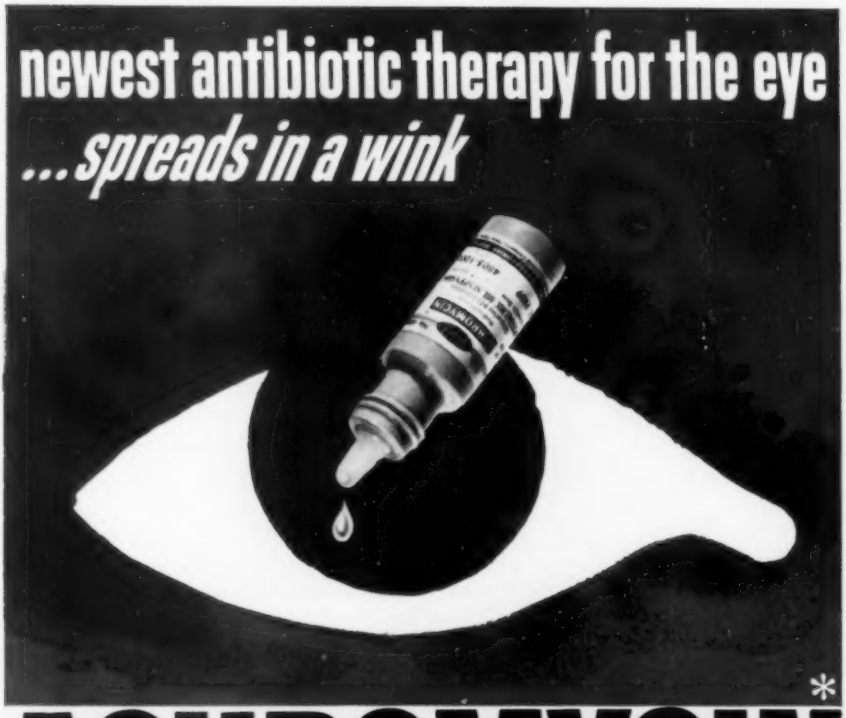

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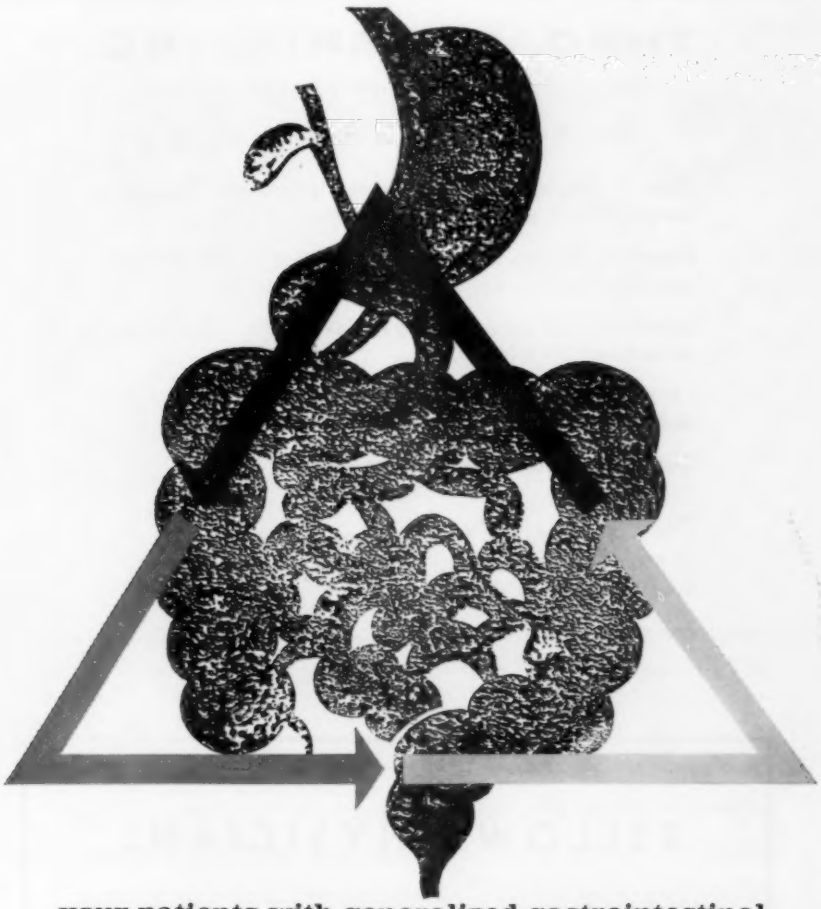

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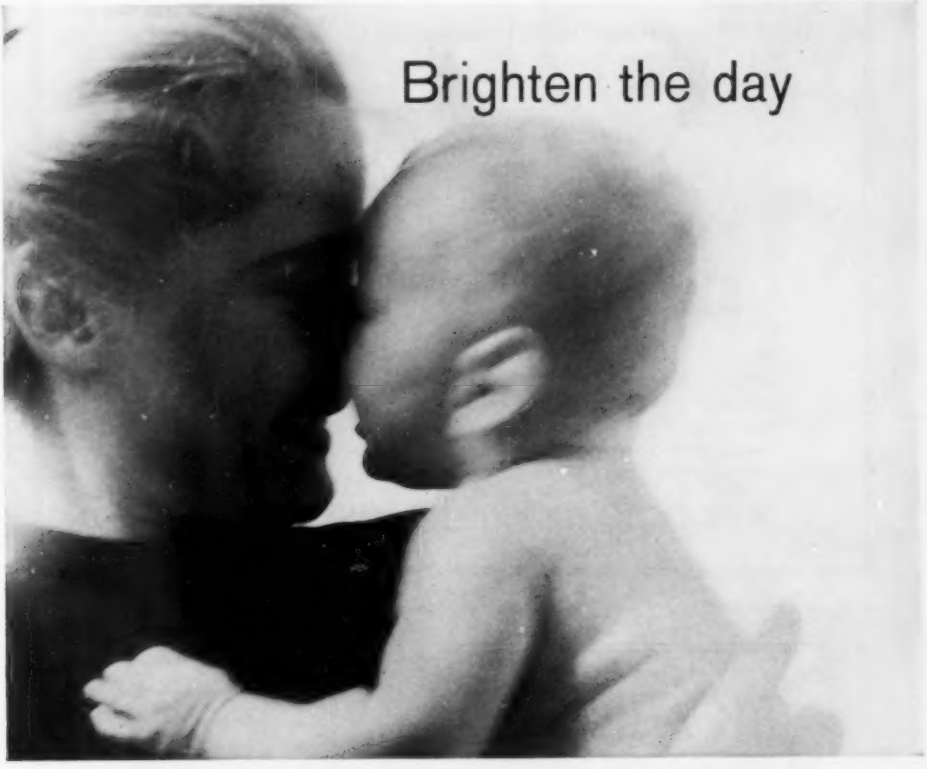

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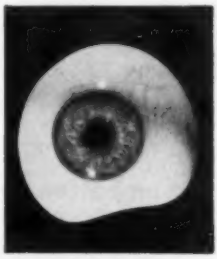

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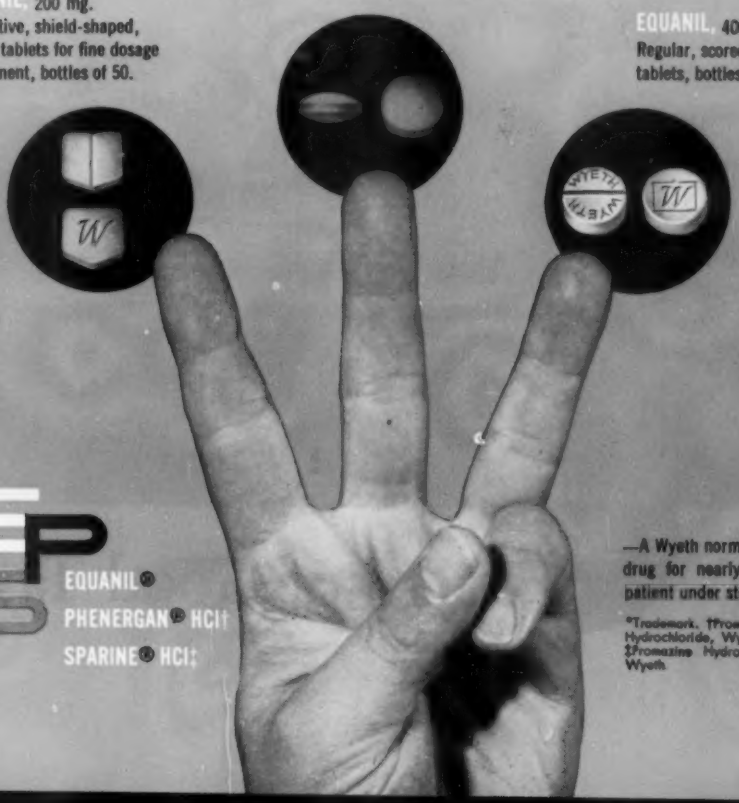

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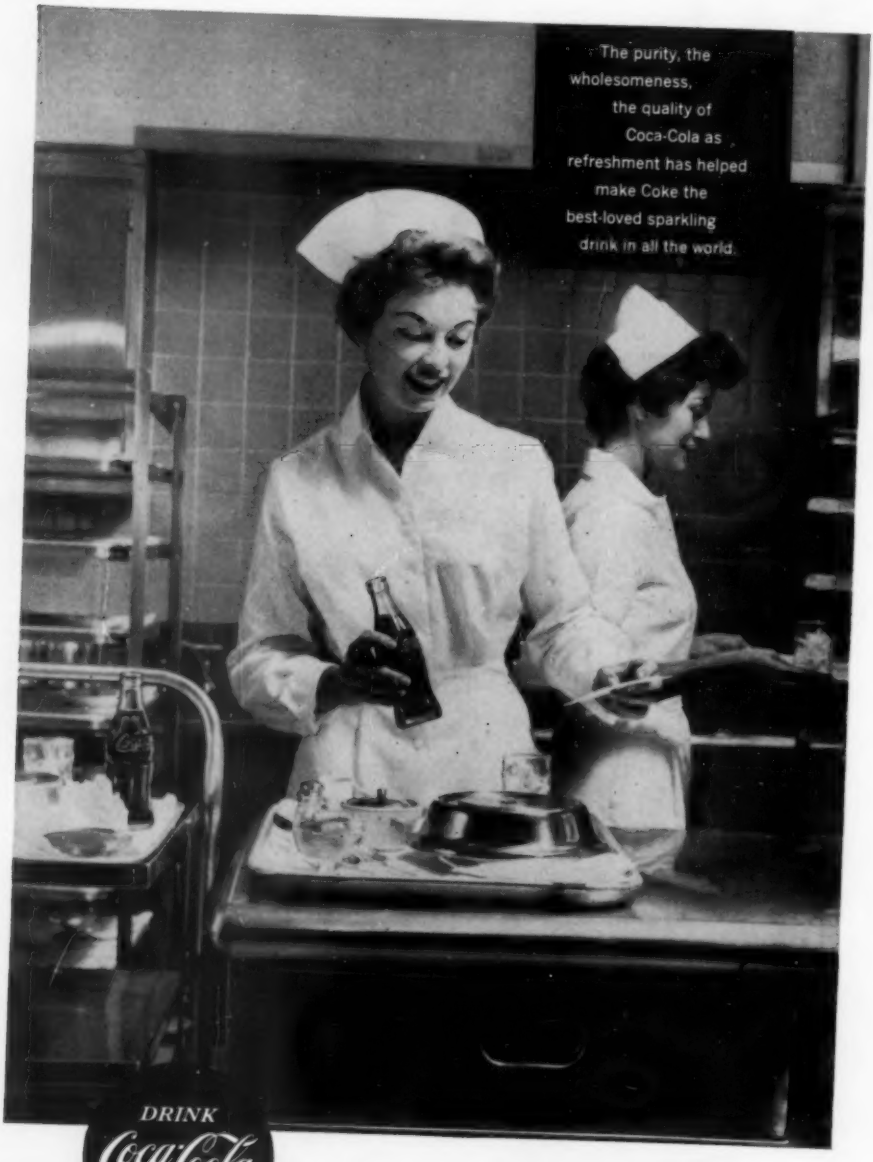
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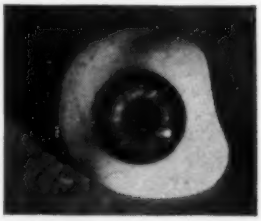

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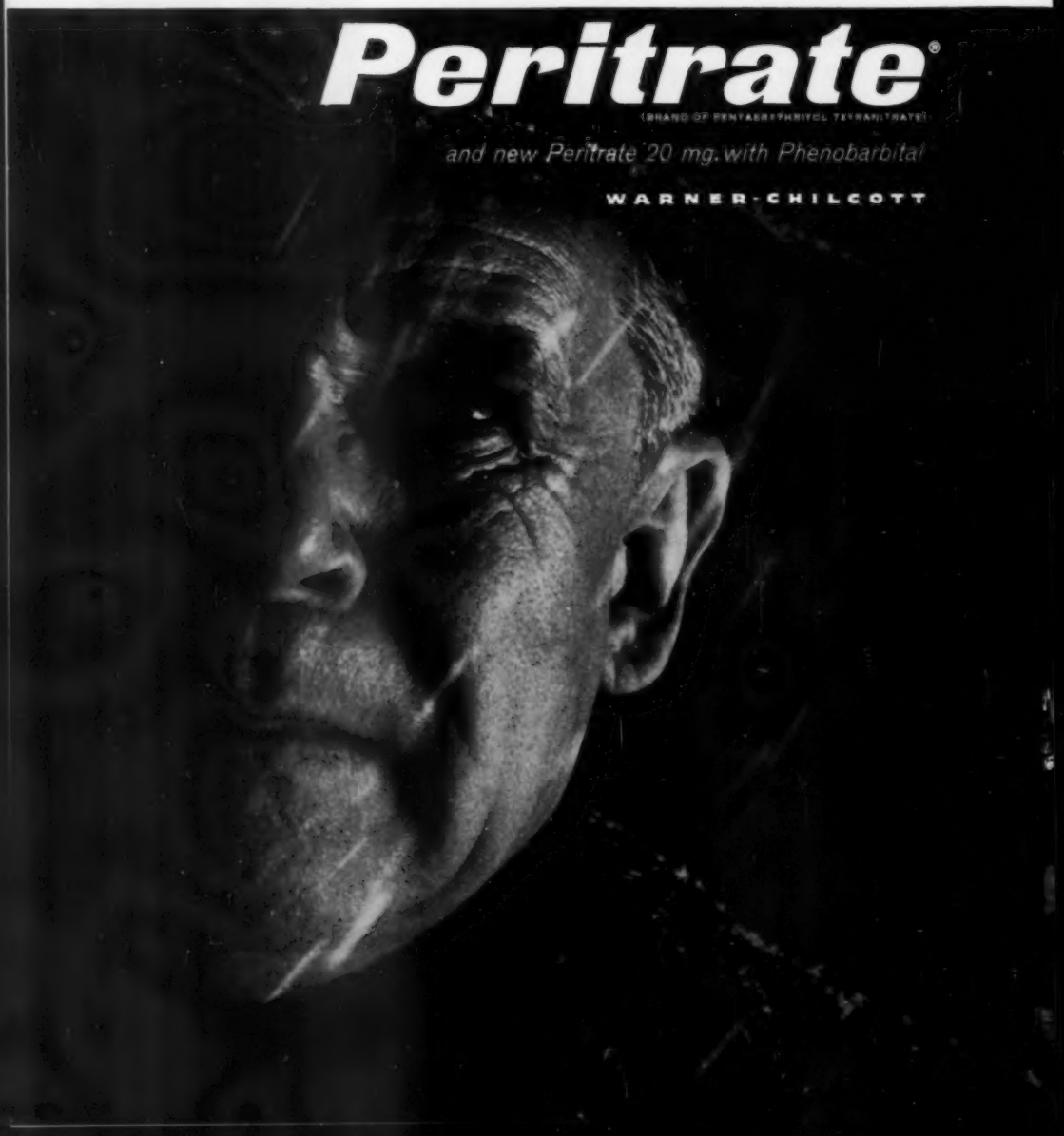

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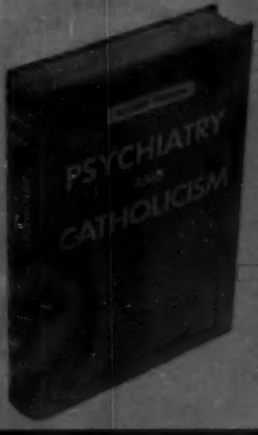

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